CLINICAL TROPICAL MEDICINE

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Editor in Chief

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Editors

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DEDICATED

To those who toil in the heat and sweat of the tropical plantations and tropically located industrial enterprises to those who enter the jungle and the desert to bring health and progress to the native inhabitants to those rural workers and village physicians whose only information on this subject must necessarily be obtained from a comprehensive manual to the medical men of the Armed Forces who enter tropical territories and seriously prepare to safeguard their troops against the diseases of the land and to those who wish to familiarize themselves with the great problems presented by the Tropics

FOREWORD

With modern methods of communication and also as a result of the large numbers of men from the temperate zones who spent considerable periods in the Tropics during World War II, tropical medicine has assumed an importance greater than at any time in the whole history of medicine. Many advances and discoveries have also been made in this field in recent years. The literature of tropical medicine is constantly being increased. Preventive tropical medicine is a matter of great urgency in our present troubled world conditions. This textbook is of particular interest in that it is largely a production of Pan American authors in that leaders in the various fields of tropical medicine in North, Central, and South America have collaborated in its production. It represents a valuable addition to the many fine works on tropical medicine. As a textbook it will be extremely valuable.

Ross T McIntire
Vice Admiral Medical Corps
United States Navy Retired

PREFACE

The Editors present to the English-speaking scientific world this book on *Clinical Tropical Medicine* written by fifty-seven authors The variety and diversity in concept opinion and method of approach apparent in every chapter of the book begin with the personal training and individualities of the Editors One (R B H G) born reared and educated in the United States with many years of European postgraduate work including studies at the Hamburg Institute of Tropical Medicine wrote from his experiences in the United States Navy and his travels Another (L B S) a son of Latin America lives works and teaches in Mexico representing the views of Central and South America Finally the third (O F) a Continental European by upbringing but an American by choice is making every effort to synthesize the teachings of his West European masters with the achievements of the New World

The freedom of expression which the Editors maintained for themselves has been reserved also for the contributors While certain requirements were necessarily observed by each writer there was no curtailment of ideas and concepts The number of pages had to be limited but not the internal arrangements of the chapters thus no objection was raised if an author wished to stress one or another part of his contribution or desired to express an unusual opinion

While the Editors believe in the great value of contributions from established authors they feel that the younger writers should also have their say It was for this reason that some authors were selected whose qualifications were ample but whose claims to international recognition had not yet been established We hope that the results will prove satisfactory

In selecting the authors of this book every possible effort was made to appoint only those with actual clinical experience with the diseases with which their writing was concerned In other words the compilation of literature and findings of a variety of experts was not what was desired rather it was desirable to have clinical and laboratory experiences recorded which came out of daily contact with the diseases in question It is not given to any expert on tropical medicine to be familiar with all the diseases of the Tropics This book pretends to be a record of specialistic knowledge

The material and scope of subject matter which should form a book on tropical medicine were much debated in preliminary discussions After serious consideration the Editors decided that climatic nutritional and transmissible diseases should be stressed with special emphasis on those which with a few exceptions such as dysenteric disorders constitute a major problem only in the Tropics Smallpox rabies coccidioidosis etc which are often included in handbooks of tropical medicine do not appear in this volume

The idea for the present book was conceived in 1944. It was originally intended to be a Pan American work. Delays in the publication carried it over into postwar years. While this necessitated bringing many chapters up to date, it also permitted the Editors to include valuable contributions from Dutch, English, and Indian authors which could not have been secured during *World War II*.

In the preparation of this type of book, there were many difficulties due to the fact that a great deal of the manuscript was submitted in foreign languages. In correcting translations, in checking dosages of drugs, references to the literature, style, spelling, etc., the admirable literary and editorial talents of our assistant, Mrs. Addine G. Erskine, must be paid a special tribute. All this, together with her careful preparation of the index, merits our deepest appreciation and thanks.

The Editors wish to express their deepest gratitude to all contributors.

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CLINICAL TROPICAL MEDICINE

CHAPTER I

INTRODUCTION TO TROPICAL MEDICINE

R B H Gradwohl

Tropical medicine has naturally always been an important part of the practice of those who dwell in tropical regions it has lately assumed an important place in the practice of many physicians who live far from the tropics since many of these so called exotic diseases may also occur in temperate zones or may be imported by reason of today s rapid communications The reader will note elsewhere (Chapter 63) important information about diseases of the temperate zone as they manifest themselves in the tropics Here and there he will find frequent reference to the diseases of the tropics as they manifest themselves in more temperate zones Again there are certain diseases which are tropical which are distinctly *not* tropical—malaria and amebic dysentery This brings us to a consideration of the meaning of the term 'tropical medicine '

Much debate has waged about the propriety of this term Col F R Dieuaide (1945) then Chief of the Tropical Disease Treatment Branch in the Office of the Surgeon General United States Army stated that there are very few true tropical diseases and that the classification of world wide diseases such as plague and cholera is quite dangerous since it may result in widespread ignorance of their nature and general lack of skill in their control Again referring to malaria which is commonly called a tropical disease it is a very important disease in the United States and is not necessarily tropical Relapsing fevers also are tropical only in small part Kala azar a so called tropical disease is very common in Peiping China a latitude of 42 degrees north definitely not a tropical area Beriberi a so called tropical disease is found outside the tropics Neither bacillary nor amebic dysentery is confined to the tropics This author believes that tropical medicine so called has only a feeble and inaccurate significance meaning at best diseases not now common in Western Europe or North America He insists upon the point that there are peculiarities of disease in relation to topography climate and the distribution of pathogenic and disease transmitting organisms such subjects are part of pathology Interrelated in many ways are the effects of social conditions as they occur in various regions of regional food habits and food supplies and of hereditary racial traits He offers the term geopathology to cover this question There is considerable reason to consider this writer's suggestions very seriously The Continental experts have used the terms 'exotic diseases' and diseases of warm countries to cover this branch of medicine In the meantime we shall continue to use the old term tropical medicine" until full debate and more appropriate conclusions are drawn therefrom

As far as the United States is concerned the need for adequate facilities for the study of tropical diseases became painfully evident with the outbreak of World War II A synopsis of prevailing conditions is to be found in a monograph issued by The American Foundation for Tropical Medicine and the Liberian Institute of the American Foundation for Tropical Medicine * This society was organized and incorporated in the state of New York in 1940 It has ever since its foundation aided in the development of broad interest in tropical medicine In its pamphlet it is stated that following Pearl Harbor, a survey by Army and Navy medical services revealed only twenty four civilian doctors in the United States available for service with sufficient background to be useful in training medical men in tropical medicine While good work was done with this limited personnel they properly stated that two additional steps would have to be taken before this country would cease to lag behind and attain a ranking position in tropical medicine (1) establishment of a graduate school like the London School of Tropical Medicine and (2) the establishment of a research center in the tropics where scientists could do research work and students could be trained in the natural environment of true tropical diseases Such a research institute has been established through a gift of Mr Harvey S Firestone Jr for the construction and equipment of a research institute in Liberia West Africa

It was stipulated that at least ten leading university medical schools in the United States should agree to utilize the Institute for research and graduate training and that the Institute facilities be made available for all who are qualified without distinction of race, creed or color

The following universities have signified their interest in participating in the Institute s program and have each designated a representative to serve on the Scientific Advisory Committee

Bowman Gray School of Medicine of Wake Forest College
Columbia University School of Medicine
Duke University School of Medicine
Harvard University School of Medicine
Howard University School of Medicine
Johns Hopkins School of Medicine
Long Island School of Medicine
Meharry School of Medicine
New York University School of Medicine
University of California School of Medicine
University of Chicago School of Medicine
University of Michigan School of Medicine
University of Pennsylvania School of Medicine
University of Southern California School of Medicine
Stanford University School of Medicine
Tulane University School of Medicine

Liberia is just two flying days from New York and offers ample facilities for the study of tropical disease The Institute aims to take up three problems (1) diseases of man (2) diseases of domestic animals and (3) production of staple food crops

Thus the development of interest and progress in tropical diseases has been given a tremendous impetus by the foundation of the Institute There remains one more step in

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the United States, and that is the organization of strong departments of tropical medicine in various university medical schools Tulane, Harvard, Michigan, Johns Hopkins, California, and others are now making this effort There is every reason to believe that the training of medical students in the future in this country will be ample and will well cover this hitherto neglected field

With reference to adequate schools for research in tropical medicine, attention is called to the School of Tropical Medicine created by joint resolution of the legislature of Puerto Rico of June 23, 1924, which transferred to the school all the properties of the former Institute of Tropical Medicine and Hygiene A plan of cooperation between the University of Puerto Rico and Columbia University of New York for the operation of the school was worked out in conferences between representatives of the two universities in 1925 and was put in operation in 1926 According to this agreement the authority to determine the educational policy of the school and to make nominations to its faculty was delegated to Columbia University, subject to the approval of the special board of trustees In other respects, the school was operated as a semiautonomous unit of the University of Puerto Rico The primary aim of the School of Tropical Medicine in Puerto Rico is research, but it also offers opportunity to study in a tropical environment the cause and prevention of that large and ill defined group of disorders known as tropical diseases and, at the same time to observe the influence of tropical conditions on disease in general Puerto Rico offers special advantages as a site for such an institution As part of the United States, the island has unusually close cultural and commercial relations with the mainland and Canada The distance from New York is only 1,330 miles, less than four days by steamer and one day by airplane The island is a logical meeting place for English , Spanish , and Portuguese speaking investigators and students

The School of Tropical Medicine of San Juan was the first of its kind to be established in the Americas This school has well equipped laboratories for bacteriology, pathology, clinical medicine, chemistry, medical mycology and dermatology, and medical zoology The laboratories are modern in construction and contain all the conveniences necessary in carrying foward a well rounded research program In addition, there are teaching laboratories of fifty student capacity for the study of bacteriology, parasitology, and clinical pathology The official publication of the School of Tropical Medicine is the *Puerto Rico Journal of Public Health and Tropical Medicine*, printed as a quarterly in English and Spanish by Columbia University Press, of New York City, in cooperation with the Insular Department of Health

Adjoining the school is the sixty bed University Hospital, devoted mainly to the diagnosis and treatment of special diseases of the tropics and operated as the school's chief teaching and research clinic The first floor is given over to a well organized clinic for the out patient department, essentially in providing the facilities necessary in the selection of cases clinical pathology laboratory and x ray and urological divisions, together with the administrative and record offices There are courses in public health, but the courses offered are planned primarily for graduates in medicine who wish special training in tropical medicine and hygiene The degree of Doctor of Medicine from an approved medical school or satisfactory evidence of adequate preparation for the courses which the applicant desires is required in each case Women are admitted on the same terms as men

The last director of this school was Prof P Morales Otero Graduates in medicine will find in the School of Tropical Medicine at San Juan, Puerto Rico the proper environment and facilities for carrying out research on all tropical diseases *

* [illegible] of Tropical Medicine at San Juan [illegible] Legislature of 1949 dissolved the [illegible] bia University and established a [illegible] using the present facilities and [illegible] usual but the main aim for the

The College of Medical Evangelists has recently announced that a School of Tropical and Preventive Medicine is to be developed at *Loma Linda Calif*. It will operate in conjunction with the School of Medicine. Medical graduates and undergraduates will be given training in tropical medicine with emphasis on preventive aspects. Special short courses will be given for nonmedical missionaries preparatory to their departure for overseas posts. Dr Harold N Mozar has been named director of this new unit. He was director of the United States Army's World War II School of Tropical Medicine for overseas forces in New Guinea and Chief of the Communicable Diseases Section of the 47th General Hospital.

Getting back to World War II, our fighting forces soon found themselves scattered over a vast territory, much of which was tropical. Acquaintance with many diseases hitherto unknown to the American military medical officer was gradually acquired. A number of important scientific studies were made in the field on malaria, schistosomiasis, amebiasis, trypanosomiasis and other tropical diseases. Special hospitals and organizations were soon formed to care for many of the victims of these diseases.

With the termination of hostilities, the important question arose as to the probability of transmission of many diseases of the tropics from the sick veteran to the healthy civilian population. Fortunately many of the usual vectors of these diseases are not ordinarily found in our country so that inoculation of new victims from residual cases seems remote. This does not obtain with water borne and food borne diseases. Nevertheless, the importance of recognition of the symptomatology of such diseases by civilian physicians is still very great. Medical education is still called for with respect to tropical diseases. Again as it has truly been said, the period of incubation of many tropical diseases is often longer than the time required to fly completely around the world, therefore the possibility of direct importation of many diseases by flying Americans or foreigners is quite manifest. A man might land in New York City and come down with a severe and comatose attack of cerebral malaria and it might be unrecognized until autopsy reveals the true diagnosis. Medical records show that this occurred twice in New York City in recent years so the need for alertness in diagnosis of such diseases still obtains. In other words every practicing physician must know tropical medicine.

As far as literature is concerned there are many excellent periodicals devoted to the study of tropical diseases notably the *Transactions of the Royal Society of Tropical Medicine and Hygiene* the *American Journal of Tropical Medicine* *The Journal of Tropical Medicine and Hygiene* (London), *Quarterly Journal of Tropical Medicine and Hygiene (Documenta Neerlandica et Indonesica de Morbis Tropicis)* (Amsterdam). There have been many excellent text books written on this and allied subjects.

My early recollection is that of an old reference book by Martin Mayer entitled *Exotische Krankheiten*. Another which was quite useful to me while working in the Hamburg Institute of Tropical Diseases was *Krankheiten und Hygiene der warmen Länder* by Ruge, Muhlens and zur Werth. The late Admiral Stitt wrote a book entitled *Diagnosis, Prevention and Treatment of Tropical Diseases* which has passed through several editions and is a classic. The late C M Wenyon of the London School of Tropical Medicine, wrote a book called *Protozoology* which gives important underlying information on this subject. My former teacher at the Hamburg Institute Eduard Reichenow, wrote with Doerflein *Lehrbuch der Protozoenkunde*. The French text by Neveu Lemaire entitled *Traite d Helminthologie Medicale et Veterinaire* is another classic. Sir Philip Manson Bahr's textbook entitled *Manson's Tropical Diseases* has passed through thirteen editions, which is sufficient proof of its great

value Z Taylor Berkovitz' *Clinical Tropical Medicine* was a valuable undertaking and so are Faust's excellent treatise on *Human Helminthology* Craig's *Laboratory Diagnosis of Protozoan Diseases* and Belding's *Textbook of Clinical Parasitology* A remarkably useful book is that by J E Ash and S Spitz *Pathology of Tropical Diseases* During the war, Mackie Hunter and Worth issued the excellent volume entitled *A Manual of Tropical Medicine* written under the auspices of the Division of Medical Sciences of the National Research Council More recently Dubois and van den Berghe the well known Dutch investigators have issued their book entitled *Diseases of the Warm Climates* Another interesting and worthwhile volume is that by L. Everhard Napier entitled *The Principles and Practice of Tropical Medicine*

We now come to the present volume which is by international authors This book was organized and thought out by the writer in conjunction with Luis Benitez Soto and Oscar Felsenfeld It was thought that a book by international authorities from men who had had actual experience with the subjects in their respective chapters would prove a valuable addition to the literature This book is intended to be a guidebook for those practicing medicine in the tropics as well as for those in temperate zones who are forced to face the issue of picking out from an assembly of temperate zone diseases those which originate in the tropics or which have been transmitted from the tropics to this and other temperate zone countries

It is a well known fact that two diseases have been brought back by servicemen returning from the Pacific Islands from the China Burma India theater and from the Middle East These two diseases are amebic dysentery and hookworm T T Mackie has stated that of the veterans treated at his School of Medicine 61 per cent had parasitic infection of which 36 per cent were amebic dysentery and 10 per cent hookworm Mackie states that he estimates there are about one million infected veterans and that it is very important to train more physicians and laboratory specialists in tropical medicine

With respect to malaria which is both a tropical and a temperate zone disease reference is made to the presidential address of E Harold Hinman President of the National Malaria Society (1949) The National Malaria Society is an outgrowth of the National Malaria Committee Hinman gives the details of the history of this organization which are very interesting because the activities of this Society are intimately bound up with the campaign against malaria in this country To summarize a resolution was adopted before the Second Pan American Scientific Congress Washington D C Jan 7 1916 as follows

> That all American countries inaugurate a well considered plan of malaria rad at and control based upon the principle that the disease is preventable to a much greater degree than has thus far been achieved and that the education of the public in the elementary facts of malaria is of the first order of importance to the country's concern

The National Committee on Malaria was then formed whose objectives were (a) to stimulate interest in malaria problems (b) to serve as a medium through which societies and individuals may become identified with the study and prevention of the disease and (c) to coordinate the efforts of these

agencies with constituted federal state and local authorities The first meeting of the Committee was held at Memphis Tenn Nov 12 to 15 1917, in conjunction with the meeting of the Southern Medical Association Subsequent meetings were held in conjunction with this Association Since malaria attains its highest level of endemicity in the United States in the southeastern section this was indeed a fortunate organizational arrangement

The National Malaria Committee met for twenty five years and was succeeded by the National Malaria Society Just a little over fifty years ago in August 1897 Ross in India discovered the mechanism of the transmission of malaria which permitted a sound epidemiologic approach to the control of this devastating disease The technics for antimosquito programs developed very promptly including utilization of petroleum oil drainage filling screening etc By the onset of World War I extensive malaria control projects had been initiated in the southern United States by the United States Public Health Service and the International Health Board and the disease was recognized as preventable

Hinman called attention to the fact that with the millions of men returning from active duty in malarious areas of the tropics there was serious apprehension that malaria in the United States which had been steadily declining might flare up in a widespread manner throughout a great portion of the United States Despite numerous relapses among veterans in areas with substantial anophelism fortunately these fears were unfounded

There has been a general decline of malaria in this country which was believed to have begun during the last quarter of the nineteenth century In a letter to Dr Paul F Russell on Dec 12 1947 the president of the National Malaria Society stated

> It is becoming evident that malaria as a public health problem within the continental United States may disappear largely within the next few years This of course does not indicate that the United States will lose any of its concern in the control of malaria for it will have to maintain a program of surveillance and emergency control within its continental borders and it is not likely that within such a brief period the interest in the control of malaria will diminish greatly in many of the tropical countries of the world in which the United States has vital interests. In view of the homogeneity of interests of the membership of the National Malaria Society which is quite unusual in view of the heterogeneity of their professional background it is believed that it would be most undesirable to countenance the possibility that our membership might disintegrate and that no adequate provision be made for retaining the professional contacts which have been so useful in the past

In reference to the future Hinman in the presidential address stated that Russell had listed six very specific reasons for insisting upon the continuing importance of malaria in the United States National defense programs must contemplate the possibility of coping with malarious areas the acute world food shortage is intensified by areas undeveloped largely because of malaria, American business is expanding into malarious countries and is concerned with the efficiency of malaria control all our imports from malari

ous countries carry a hidden "malaria tax," our exports to malarious countries are restricted because malaria depresses the economic levels and finally there is a need to prevent the resurgence of malaria in our own country

It is safe to conclude that while malaria is definitely on the downgrade in this country the above remarks of Hinman indicate that we must continue to be alert in destruction of anophelism and in carrying out preventive measures in all parts of the world with which we are economically and culturally concerned

It is difficult to realize the extent of parasitic disease in this world both in and out of tropical areas The presidential address of Dr Norman R Stoll, of the Rockefeller Institute for Medical Research Princeton N J before the American Society of Parasitologists Dec 27 1946 entitled "This Wormy World" gives data that Stoll compiled on the prevalence of parasitic disease that will astonish the uninformed

The following figures are given by Stoll It is generally taken as a statistical fact that there are about 2 166 million people on the entire globe Taking Trichinella as a well known parasite there are about 500 million people in Europe including Russia with an average diaphragm infection rate of as low as 1 per cent (and this is much higher than prewar indices) that would mean that there are about 5 million cases in that area There are about one million cases in Central and South America Mazzotti of the Institute of Tropical Diseases and Public Health of Mexico estimates that there are 12 per cent Trichinella infections in Mexico City In Canada it is estimated that there are about 100 000 cases and in the United States one in six Americans is affected or about 21 million cases Hall and Collins emphasized that "the United States has the greatest problem of trichinosis of any country in the world" Quoting again from Stoll there are 39 million *Taenia saginata* (the beef tapeworm) infections most ascribed to Africa and the U S S R but less than 3 million *Taenia solium* (pork tapeworm) infections with nearly a half in Russia There are less than 100 000 cases of hydatid infection with South America leading There are 20 million cases of *Hymenolepis nana* infection two thirds of them in Asia There is a world total of 10 million cases of *Diphyllobothrium latum* infection with 3 million in the Baltic littoral northern Russia and U S S R in Asia

Of fish transmitted trematodes there are 19 million cases of *Clonorchis sinensis* (liver fluke) infection confined to Asia and there are indications of one million cases of the related *Opisthorchis felineus* infection confined to fisher folk in East Prussia the Dnieper River basin and northern Sverdlorsk in Asiatic U S S R There are about a few hundred thousand cases of fishborne intestinal flukes the Metagonimus and Heterophyes and an equal number of Echinostoma and Gastrodiscoides

The large intestinal fluke *Fasciolopsis buski* confined to Asia is responsible for 10 million cases about half of which are in the Chekiang endemic center There are no more than 100 000 cases of *Fasciola hepatica* infection There are about several hundred thousand cases of *Dicrocoelium dendriticum* infection in man found especially in the Stalingrad and Transcaucasus regions Regarding

Paragonimus westermani cases there are about 3 million infections of this lung fluke in Asia and a few thousand in West Africa. Of these trematode infections altogether there are about 34 million cases. The schistosomes are responsible for more than three times as many additional trematode infections with *Schistosoma japonicum infections the most numerous*. There are about 46 million cases of this infection. It is endemic in the Yangtze valley. Twenty per cent of the inhabitants of Chinese provinces in this valley are infected, 10 per cent in other Chinese provinces and Japanese prefectures and 30 per cent *in the Philippine Islands of Leyte, Samar, Mindoro and Mindanao*—a grand total of 46 million people. In some places in East Africa there is a 50 per cent incidence. Scott estimates 6 million are infected in Egypt; there are about 200 000 cases in the Near East, a few thousand in Europe, a grand total of 39 million bilharzia infected people.

Schistosoma mansoni is the most dispersed of the three schistosomes of man. It is found in the equatorial region of Africa, a band of infection from northern *Nigeria westward, with Scott's 3 million cases in Egypt, making a total of 23* million in Africa. There is a third of a million in the West Indies, 30,000 cases in Venezuela according to Scott, and nearly 6 million in northeastern Brazil. This gives 29 million cases altogether, or 114 million cases with all three schistosomes.

Regarding the guinea worm and the filariids there are about 27 million cases of *Dracunculus medinensis* in India. In Afghanistan, Iran, Arabia and southwestern U S S R in Asia there are 5 million more cases of the "fiery serpent." The African endemic areas furnish 15 million cases. The world has 48 million guinea worm cases.

Onchocerca is localized on the Pacific slopes of three states in Guatemala and two states of Mexico. *It is found in Africa in the zone from Sierra Leone* eastward. The world total does not exceed 20 million cases of infection.

There are about 7 million cases of *Mansonella ozzardi* infection in Central and South America. There are 27 million cases of *Acanthocheilonema perstans* infection in Africa, South America and Dutch New Guinea. There are 13 million cases of *Loa loa* infection in Africa. These four filarial forms conveyed by Simulium, Culicoides and Chrysops parasitize 67 million people.

As for the Wuchereria, Stoll does not distinguish in his analyses between *Wuchereria bancrofti* and *Wuchereria malayi*. They and their mosquito vectors are found throughout the tropical world. He believes that all the endemic areas are filariated, thus giving an infection rate of 758 million people, about one-third of the population of the globe.

Coming nearer home we may discuss a very common worm found in great numbers in this country, namely the Enterobius. In North America and Europe including U S S R the total number of infections reaches 18 and 87 million.

Some nematodes contribute over half of the helminthiases of man. Discussing *Ancylostoma duodenale* Stoll showed that by education and actual attack the number of hookworm infected Americans had decreased from 4½ mil

lion to 1¾ million between 1910 and 1935 Our present figures on hookworm infections are as follows from one to a few million in Oceania Europe North America and the USSR up to 359 million in Asia including Japan the Philippines and Dutch East Indies The total number of cases for the world is 457 million

Ascaris infections in North America total 3 million in Central and South America 14 times as many in Africa nearly 60 million in the world 644 million—these with hookworm representing about half of man s helminthiases The world total Trichuris infections comes to 355 million Strongyloides infections in Asia and Central and South America make a world total of 35 million cases

After surveying and emphasizing these figures Stoll estimates that it is possible to reduce the 3 000 million human cases of helminthiases by the year 2000 when the world population will reach the figure of 3 300 million inhabitants by the following ways

1 By applying and strengthening the teaching of the nuclear principles that apply in the field of parasitology

2 By encouraging by precept and example a shortening of the usual lag period in getting acceptable improvements in ideas through to where they will do the most good and by being less tolerant when the lag seems unnecessarily long

3 By sharpening the tools for attacking the helminthiases of man Against the intestinal worms education sanitation and treatment must be considered New chemotherapeutic preparations are desirable

These figures and conclusions of Stoll still further prove the necessity for medical men of all climes to acquaint themselves with the problems of tropical medicine

Insofar as tropical medicine and diseases of the temperature zone are concerned I cannot refrain from quoting (paraphrasing) at great length from Sir Philip Manson Bahr s presidential address before the Royal Society of Tropical Medicine and Hygiene in 1947 In this address entitled The Practice of Tropical Medicine in London Sir Philip Manson Bahr in most detailed manner narrated the types of cases about which he had been consulted in London the difficulties in diagnosis and the manner in which diseases of the temperate and tropical zones were intermingled and mistaken one for the other He called attention to the fact that pyonephrosis may resemble malaria He cited a case of a man who came by air from India to London because of malaria associated with renal symptoms In this case the true diagnosis was made the patient responded to blood transfusions and mandelic acid returned to India and remained well The splenomegaly mistakenly attributed to malaria was probably due to *Escherichia coli* septicemia In a number of cases suspected of malaria some other disease condition was found He reported a case of a woman who was referred to him because of ptosis of the spleen She had spent most of her life in India and had suffered severely from malaria She was treated in England with Atabrine and was highly

pigmented The large hard moveable mass with a sharp edge jutting out at the level of the umbilicus and extending *into the left iliac fossa* proved to be an inoperable gastric carcinoma He called attention to the fact that malarial cachexia may be mistaken for Addison's disease Manson Bahr further spoke of the effects of quinine *producing an acute hemolysis* which may be a precipitating factor in attacks of blackwater fever He warned practitioners that *kala azar* while *infrequent* in European patients may actually be seen far away from its *normal habitat* *In these cases* the appearance of the patient is different from that of the malaria patient The eye has a different look — not quite the shining penetrating gaze of the patient with malarial cachexia The splenic dullness *extends above* the costal margin and there may be some edema of the legs He reports a case of tuberculosis which resembled kala azar

Sir Philip Manson Bahr formulated some generalizations about amebiasis as it is seen in temperate zones such as London England First there exists a good deal of wishful thinking which tends to magnify the numbers of potential amebic cases Second there exists a wishful willingness to ascribe pathogenic properties to any species of ameba found in the feces Third acute abdominal pain and extreme meteorism are not features of intestinal amebiasis Fourth acute onset febrile attacks and vomiting are not characteristic of amebic dysentery which is usually apyrexial Fifth severe anemia of the pernicious type is not an accompaniment of amebic dysentery Sixth as compared with bacillary dysentery tenesmus is infrequent while loss of weight is not a marked feature Lastly he states that the presence of *Endamoeba histolytica* cysts in the feces does not always completely account for the whole clinical picture as is amply demonstrated in this address

He made a number of other interesting observations pertinent to the *question of the practice of medicine in the temperate zone* and he took up the question of tropical nontropical disease differentiation

Relative to tropical sprue he reported a number of cases referred to him as *gastric carcinoma duodenal ulcer cholecystitis* Addison's disease and pernicious anemia *all of* which were affected with tropical sprue

Sprue may be mistaken for Addison s disease for cholecystitis and for malignant diseases *Tropical ulcer is infrequent* in Europeans and when seen must not be mistaken for anything else He calls attention to the occurrence every now and then of cases of leprosy which may be extremely chronic in its *course and may have a latent period of over thirty years* before the lesions become obvious He warns of the necessity of diagnosis of helminthic infections which are usually symptomless and require *concentration methods of the feces for demonstration* of the eggs A most interesting case of *Clonorchis sinensis* infection was recorded in a Chinese politician with a long history of cholecystitis with fever pain and *jaundice* *Cholecystograms* revealed pigmented stones In addition he was a confirmed diabetic and operation was refused point blank As Sir Philip Manson Bahr put it *"Eventually he became the* Japanese puppet *at* Nanking so that in retaining his gall bladder he lost his

head!' Infections with *Loa loa* with Calabar swellings have been seen by Manson Bahr in London in a case originating in the tropics

His address from which I have quoted is a chronicle of the ups and downs of consulting practice in tropical medicine in London One must remember that the same thing might occur in New York Chicago St Louis or San Francisco Thus one must not confuse tropical medicine with temperate zone medicine and vice versa An even keel an understanding of clinical medicine in its entirety, is always necessary

TABLE I ROUTINE IMMUNIZATIONS

(From Technical Bulletin 114 by permission of the Department of the Army)

AGENT	NUMBER OF DOSES	INITIAL SERIES		STIMULATING DOSE	
		INDIVIDUAL DOSE	INTERVAL BETWEEN DOSES	WHEN INDICATED	AMOUNT
Smallpox vaccine	1	Contents of one capillary tube		Every 3 years with in 1 year prior to departure for over seas areas and in presence of the disease*	Contents of one capillary tube
Typhoid paratyphoid vaccine	3	First dose 0 5 c c second dose 1 0 c c third dose 1 0 c c	7 to 28 days	Annually and in the presence of the disease	One dose 0 5 c c
Tetanus toxoid (plain)	3	Each dose 1 0 c c	Minimum of 21 days	One year after initial series and upon occurrence of wounds or burns as directed by the medical officer	1 0 c c as booster dose

*f ditor a ... are actually occurring and ... the time of the last vaccir ... ination has not been caret ... vaccinati n, if within a p ... or a well defined accele ... he previous reaction was ... to ensure against the p ...

In concluding this chapter as an introduction to this subject as handled by our distinguished staff of authors I should like to call attention to a few generalities so well set forth in a pamphlet entitled *Health Hints for the Tropics* by Strode et al In it are discussed climate water food insects and insect vectors of disease immunization and miscellaneous hints The pamphlet contains much of value The authors warn tourists to take a middle ground when visiting the tropics one between the glamorous attitude and that of looking upon visiting Africa as visiting the white man s grave It is recommended that simple rules of health be followed care exercised in the choice of food and drink and physical defects removed before going to the tropics One must readjust himself to heat light and humidity and must remember above all that moderation in all things is the keystone of successful living in the tropics He should be especially careful about the water he drinks about the water he bathes in and the water used for laundering Wading swimming or bathing in places

where schistosomes are present, such as fresh water streams, lakes, marshes rice paddies, must be avoided. *Food contamination* must be looked for and avoided. Canned food offers a safety material for nutrition. Food handlers must be inspected. The vectors of disease notably, mosquitoes which transmit malaria and those which carry dengue fever, yellow fever, and filariasis, must be considered very seriously. One must remember that sandflies, fleas, ticks, mites, lice, tsetse flies and the reduviid or "kissing bug" may carry tropical diseases.

TABLE II. IMMUNIZATIONS REQUIRED FOR TRAVEL TO CERTAIN OVERSEAS AREAS (IN ADDITION TO ROUTINE IMMUNIZATIONS)

(From Technical Bulletin 114 by Permission of the Department of the Army)

AGENT	NUMBER OF DOSES	INITIAL SERIES: INDIVIDUAL DOSES	INITIAL SERIES: INTERVAL BETWEEN DOSES	STIMULATING DOSE: WHEN INDICATED	STIMULATING DOSE: AMOUNT
Typhus vaccine	2	1.0 cc each	1 week	At 4- to 6-month intervals in presence of danger of epidemic (louse-borne) typhus	1.0 cc
Cholera vaccine	2	First dose, 0.5 cc; second dose 1.0 cc	1 week	At 4- to 6-month intervals in presence of danger of cholera	1.0 cc
Yellow fever vaccine	1	0.5 cc of the proper dilution		Every 4 years, if in yellow fever endemic area	0.5 cc of the proper dilution
[illegible]	[illegible]	[illegible] cc	[illegible]	[illegible] ho ... of [illegible] plague	1.0 cc in ... ses ... ry

*Indicated in the presence of known cases.

TABLE III. DOSAGE OF IMMUNIZING AGENTS AND AGE OF ADMINISTRATION, FOR CHILDREN TRAVELING OUTSIDE THE UNITED STATES WHEN INDICATED FOR AREA OF DESTINATION

(From Technical Bulletin 114 by Permission of the Department of the Army)

IMMUNIZING AGENT	DOSAGE	AGE LIMIT
Smallpox vaccine	As for adults	All children regardless of age
Typhoid paratyphoid vaccine	Usual number and interval between inoculations; volume of each dose reduced according to weight (e.g., one-half adult dose for a child weighing 50 pounds)	Children over 1 year of age
Typhus vaccine	Usual number and interval, dosage reduced according to weight	Children over 1 year of age
Cholera vaccine	Usual number and interval, dosage reduced according to weight	Children over 3 months of age
Yellow fever vaccine	Usual full dose	Children over 3 months of age
Diphtheria toxoid	Usual full dose (either alum precipitated or fluid toxoid may be used, alone or in combination with other agents such as tetanus toxoid or pertussis vaccine)	All children between 3 months and 15 years of age

Spiders must not be overlooked or disdained

In this pamphlet are given three tables relative to immunization which are reproduced here for the information of those about to proceed to the tropics

One must especially look out for skin diseases in the tropics The skin must be especially cared for daily baths with thorough drying of the skin in the arm pits crotch beneath the breasts and between the toes

In the tropics one must be food conscious heat conscious and insect conscious

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CHAPTER 2

A GENERAL CONSIDERATION OF THE PROTOZOA

ENRIQUE BELTRÁN

HISTORY

Because of the small size of these organisms protozoa were not seen by man until he learned to use magnifying lenses Anthony van Leeuwenhoek is generally credited with the discovery of protozoa and is justly regarded as the "father of protozoology"

After Leeuwenhoek's work, the study of protozoology advanced rapidly, especially with regard to free living organisms *Parasitic protozoa, however, did not at first excite great interest, although various isolated observations of these forms were made* It may be said that *medical and veterinary protozoology did not emerge as a branch of science until the end of the nineteenth century* Among many important contributions to this field may be mentioned the discovery of *Endamoeba gingivalis* by Gros in 1849, the first reported ameba of man, of *Endamoeba coli*, by Lewis in 1870 of *Endamoeba histolytica* by Lösch in 1875 in Russia Lewis, in 1878 observed the first *trypanosome in a mammal, in the blood of a rat* It must not be forgotten that *the first pathogenic microorganism studied by Pasteur was a protozoan (Nosema bombycis)* the cause of pebrine in silkworms

These observations did not [illegible] interest in the subject until the discovery by Laveran in 1880, in Algeria of [illegible] as well as the confirmation of knowledge with [illegible] finitely laid the basis for medical protozoology, this came a [illegible] present century, the work of Schaudinn playing a brilliant part

GENERAL CHARACTERISTICS OF PROTOZOA

Protozoa are usually microscopic organisms They are single cell organisms (Fig 1) This permits their differentiation from metazoa, or higher forms which are composed of more than one cell

Some protozoa are so small that they scarcely attain a size of one micron, as for example Leishmania or Babesia others as Nyctotherus or Opalina may *be several hundred microns* Some free living protozoa, such as *Spirostomum ambiguum*, may be as *large* as *2,000 microns* and are visible to the naked eye

The shapes of *the* protozoa vary *greatly* spherical (Halteria), oval (Holophrya) *changing forms* (*Amoeba*), *bell* shaped (*Vorticella*), *etc*

Some lack firmness of body to such extent that they continually undergo changes in shape, others show more resistance, either because their cytoplasm is firmer or because they are enveloped in a rigid membrane Occasionally especially *among* the free swimming forms they develop true shells or carapaces composed of various substances (*chitin*, calcium, and silicon salts, etc)

All protozoa have a more or less thin membrane which envelops the body In some (Infusoria) it is thick enough to be easily seen In others (Mastigophora and certain Sporozoa) it is thinner In some (Sarcodina) it is so thin that it is very difficult to observe For *this* reason, it was formerly thought th there were some protozoa *not* provided with a membrane, *these* were term

"naked" With the more modern methods of microdissection the existence of a membrane however thin it might be has been definitely proved in animals which once were thought to lack such a membrane A membrane no matter how thin plays a most important triple role retention protection and osmosis

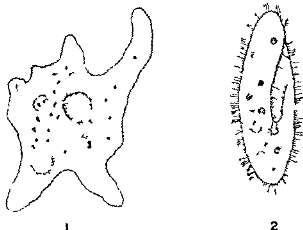


Fig 1.—Diagrammatic representation of an ameba 1, and a paramecium, 2 showing the unicellular character of protozoa (Original drawing of T … de Beltrán.)

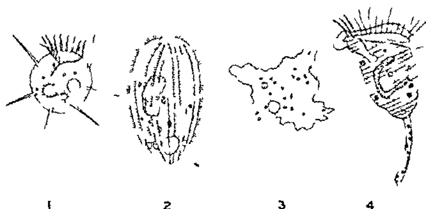


Fig 2.—Diagrammatic representation of various forms of protozoa 1 Halteria 2 Holophrya 3 Ameba 4 Vorticella (Original drawing of T G de Beltrán.)

As in every cell the cytoplasm is composed of a gelatinous and semifluid mass which can usually be differentiated into two parts an outer layer, slightly granular and relatively firm called the *ectoplasm*, and the central mass more fluid and granular which is the *endoplasm* In addition to vacuoles the cytoplasm in a great majority of protozoa also contains nutritional reserves metabolic products mitochondria Golgi apparatus, and other structures that are seen in the cytoplasm of the cells of metazoa

The nucleus is situated in the endoplasm Fundamentally it may be either (1) *vesicular*, when it presents an enveloping membrane filled with

nuclear fluid in which chromatin granules are observed, and generally a corpuscle more or less central called *karyosome (endosome)*, or (2) *compact*, with the chromatin granules so compressed one against the other that only a uniform mass is seen within the membrane In certain protozoa one does not see nuclei of one of the types mentioned but only a series of chromatin granules perhaps combined with other substances scattered throughout the cytoplasm, in such cases we speak of a *diffuse nucleus* In Infusoria we observe a peculiar double or dimorphous type of nuclear apparatus, made up of two distinct elements called *macronucleus* and *micronucleus* respectively

Some protozoa pass the greater part of their lives in a sedentary position because they are devoid of means of motility The majority, however, are endowed with active locomotion that may be carried on by means of *pseudopodia*, which are variable and transitory expansions of the body, *flagella*, which are vibratory appendages whip like long but not numerous, and *cilia* which are also vibratory appendages smaller and more numerous than flagella

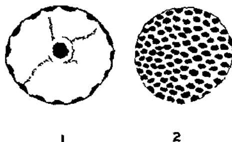


Fig 3 —Types of nuclei of protozoa (schematic) 1 vesicular 2 compact. (Original drawings of T G de Beltrán)

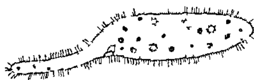


Fig 4 —Diagrammatic representation of *Dileptus anser*, showing the diffuse type of nucleus (Original drawing of T G de Beltrán)

The large majority of free-living protozoa and a number of the parasitic protozoa derive their nourishment by ingesting animal or vegetable particles this form of nutrition is called **holozoic** Other protozoa derive their food from organic substances which have been dissolved and partially processed, these substances are absorbed through the membrane Last there is a group of chlorophyll bearing flagellates which are able to synthesize organic material from inorganic after the manner of plants this method of nutrition is the **holophytic** type This last curious group is difficult to interpret so that botanists and zoologists are in dispute about them some considering them to be plants others classifying them as animals

Reproduction may be by division of the individual to form two entities of similar size **binary fission**, or by division of the individual into several entities

of similar size, **multiple fission**; or the animal may separate a small part of its body to form a new individual, **budding**

In the process of multiplication, the nucleus begins to divide into two or more portions and next the cytoplasm divides Division of the nucleus in protozoa was formerly described as amitotic It has been observed, however, that protozoa present forms of mitosis that are more or less similar to those observed in the cells of metazoa Moreover, in many protozoa, we observe sexual phenomena that are sometimes very complex

The protozoan life cycle frequently presents vegetative forms, which carry on all the functions necessary to life, and cystic forms, which permit the organism to resist adverse environmental conditions under protection of the cyst wall Occasionally the cyst may also be a form of reproduction, the organisms multiplying within the cyst

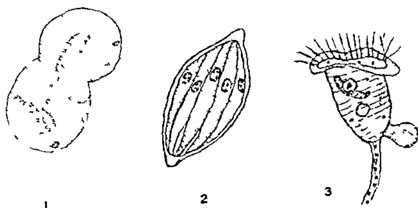


Fig 5—Diagrammatic representation of the different types of cellular reproduction of protozoa *1* binary fission (Nyctotherus) *2*, multiple fission (Monocystis) *3*, budding (Vorticella) (Original drawing of T G de Beltrán)

Some parasitic protozoa pass their entire life within the host, from which they may be directly transmitted to another (*Endamoeba gingivalis* or *Trypanosoma equiperdum*), some live within the host and leave in the form of cysts, in which form they infect new persons or animals (*Endamoeba histolytica* or *Giardia lamblia*), last, there are some which must pass successive stages of their existence in different hosts (*Plasmodium vivax* or *Trypanosoma gambiense*)

CLASSIFICATION

Protozoa are classified as follows

Class Mastigophora Provided with flagella as organs of locomotion, vesicular nucleus most often reproduction by longitudinal binary fission Free living and parasitic

Class Sarcodina Provided with pseudopodia as organs of locomotion, vesicular nucleus division by binary fission, multiple fission, or budding, sometimes with elaborate shells or carapaces Free-living and parasitic

Class Infusoria Provided with cilia as organs of locomotion at least during certain phases of their existence, dimorphic nuclear apparatus, the nuclei of which may be vesicular or compact, *exhibiting in the life cycle a special sexual phenomenon termed conjugation* Free living or parasitic

Class Sporozoa Devoid of special organs of locomotion and consequently having stationary habits, with rare exceptions, reproduction by multiple fission life cycle complicated, sometimes in different successive hosts Exclusively parasitic

ECOLOGY

Protozoa, with rare exceptions, may present two forms *trophozoites*, which move and obtain their nourishment actively, and *cystic forms*, which are surrounded by a protective envelope and can thus withstand adverse conditions

Trophozoites require a high degree of humidity in order to subsist Most of them require a liquid medium, or at least sufficient moisture Drying, even though not extreme, causes death of any protozoan in its vegetative form

Cysts, within which the organism maintains a latent existence (with the exception of the phenomena of multiplication which occasionally may be observed in this phase), have a markedly greater resistance to external destructive elements and particularly to drying because of their enveloping cover Cysts of protozoan parasites of man are sensitive to drying although they are more resistant than the trophozoites

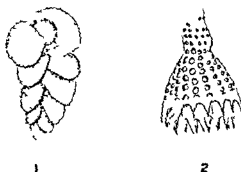


Fig 6.—Types of shells formed by protozoa 1, calcareous shell of a foraminifer 2, siliceous shell of a radiolar (Original drawing of T G de Beltrán)

Many forms of protozoa easily accommodate themselves to changes in the medium in which they live However, in each particular medium there is observed a predominance of certain species and a habitual association with other species, so that one may speak of *ecologic centers* Calkins (1933) has enumerated the six chief forms according to adaptations to specific media aquatic, semiterrestrial, terrestrial, sapropelic, coprozoic, and parasitic forms

From the medical standpoint the last two forms are most important The cysts of **coprozoic forms** can pass without modification through the digestive tract of man and animals passing from the body of the host in the excreta in which, environmental conditions being favorable, further development into the trophozoite from may take place These forms may be confused with parasitic forms whereas they are merely incidental elements in transit through the digestive tract

Parasitic forms are those which habitually live upon or within other organisms and which can present many stages in their adaptation to parasitic existence. Less thoroughly adapted forms are those of ectoparasites, as for example, *Hydramoeba hydroxena*, which lives on the ectodermal cells of the hydra. *Ichthyophthirius multifilus*, an infusorian parasite of fish, is sometimes a true ectoparasite on the skin of the fish, while at other times it is beneath the skin where it forms abscesses; it could be considered as an intermediate between ectoparasites and endoparasites.

Endoparasites also may exist in various stages. Sometimes the parasite lives simply in the cavities of the host when it is termed *coelozoic*, such as *Endamoeba coli* in man. Others, as *Endamoeba histolytica*, penetrate into the tissues and are called *histozoic*. Finally some not only enter the tissue, but localize within the cells themselves, as *Leishmania braziliensis*, in which case the parasitic form is termed *cytozoic*.

BIOLOGIC AND ECONOMIC IMPORTANCE

Protozoa breeding in fresh or salt water frequently constitute the principal food for larger animals. Thus directly or in their role as food for other larger forms they may be of definite economic importance.

As protozoa in the ocean provided with shells die, their shells drop to the bottom as sedimentary formations and through geological changes produce chalk, infusorial earth, silica sand, etc. Various industrial uses, filters, polishing powders, etc., give them economic value.

In humid soil there are masses of protozoa, principally sarcodines and mastigophores, the biological significance of which is not definitely known, but which in their association with bacteria living in the same medium certainly play an important part in the agricultural characteristics of the soil.

But if the foregoing aspects of these forms are important, their significance in relation to man is still more important if we consider them in their association with other living organisms.

In the ensuing chapters will be found detailed information concerning the principal protozoa that are parasitic to man, as well as the diseases which they cause and the most adequate means of prevention and cure.

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CHAPTER 3

INTESTINAL PROTOZOA OF MAN

ENRIQUE BELTRÁN

In the digestive tract of man there can be found various protozoa Some cause disturbances, while others appear to be purely commensal, with no pathogenic significance

Protozoan parasitism of the human intestine presents many very interesting problems For more detailed information, the reader is referred to Dobell and O'Connor (1921), Hegner (1927), Lynch (1930), Gradwohl and Kouri (1948), and Beltran (1948), or for particular problems to Dobell (1919) and Craig (1911, 1934, 1944), etc

We shall discuss the intestinal protozoa of man by treating separately the members of each of the four protozoan classes

SARCODINA

Sarcodina are characterized by *locomotion through transitory and variable extensions of the body* called *pseudopodia*

The group is *very extensive and includes many free living forms*

One of the five orders into which the class is divided is the order Amoebida, characterized by lack of shells and by formation of pseudopodia which are wide and variable, called *lobopodia* *Amoeba proteus is one of the better known representatives of this order*

Sarcodina which inhabit the human intestine are generally designated as *intestinal amebae* and are closely related to *Amoeba proteus* None belong to the genus Amoeba but to other genera

Parasitic amebae of man are small forms which do not exceed some 50 microns for the largest, with two exceptions, they may be found *in the trophozoite as well as in the cystic form*

These parasites are, at the present time, considered as belonging to six different species distributed into four genera Endamoeba, Endolimax, Iodamoeba, and Dientamoeba The principal characteristic for differentiation is the nucleus

The nucleus of all intestinal amebae is, as in all the Sarcodina, of the vesicular type In the genus Endamoeba the nucleus displays peripheral chromatin granules that are more or less regular, according to the species From this peripheral chromatin, fine granular filaments radiate toward a central *or excentric karyosome (endosome), usually with a rounded appearance* *In properly stained specimens*, one can distinguish one or more central granules deeply staining embedded in a matrix with less chromatic affinity The genus Endolimax is generally described as having a nucleus which lacks the peripheral chromatin However, some authors (Stabler, 1932) mention the presence of chromatin granules which are adherent to the membrane and *which may be observed under certain conditions* Within *the nucleus is a karyosome* (endosome), generally of irregular form, large, *and adjacent or adherent* to the outer wall of the nucleus In the genus Iodamoeba

the peripheral chromatin is absent and the large, spherical karyosome is centrally located. Under usual conditions of observation, this karyosome is seen as a uniform mass, but in very good preparations there can be seen a central mass, deeply stained, surrounded by a series of small granulations with weaker affinity for dyes, described by some authors as "pearls" The genus Dientamoeba has a nucleus without peripheral chromatin and with a karyosome formed of various large and irregular granules, deeply stained, generally situated in the center, and embedded in a matrix with poor staining qualities, frequently irregular in form, the name of the genus (Greek *di*, two) alludes to the fact that two nuclei are found in many of the trophozoites

Sarcodina which inhabit the human digestive tract are ***Endamoeba histolytica*** (Schaudinn, 1903), ***Endamoeba coli*** (Grassi, 1879), ***Endamoeba gingivalis*** (Gros, 1849), ***Endolimax nana*** (Wenyon and O Connor, 1917), ***Iodamoeba williamsi*** (Prowazek, 1911), ***Dientamoeba fragilis*** (Jepps and Dobell, 1918)

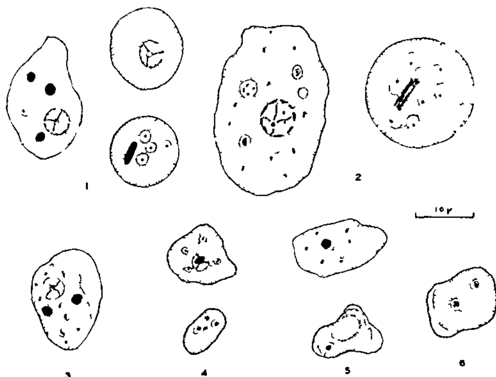


Fig 7—Parasitic amebae of man schematic representation 1 *Endamoeba histolytica* (trophozoite precyst and cyst) 2, *Endamoeba coli* (trophozoite and cyst) 3 *Endamoeba gingivalis* 4 *Endolimax nana* (trophozoite and cyst) 5 *Iodamoeba williamsi* (trophozoite and cyst) 6 *Dientamoeba fragilis* (Original drawing by T G de Beltrán)

Although the six species listed here are considered correct without exception some authors accept the existence of further species, the most frequently cited being ***Entamoeba hartmanni*** Prowazek, 1912, ***Entamoeba minuta*** Elmassian 1909 ***Entamoeba tetragena*** Viereck 1907 ***Entamoeba dispar*** Brumpt, 1925, ***Councilmania lafleuri*** Kofoid and Swezy, 1921 ***Karyamoeba falcata*** Kofoid and Swezy 1924 but these seem to be simply synonyms of the generally accepted species

There is also another noteworthy discrepancy with respect to the correct designation of species, the discussion centering principally upon the justification for using the generic name Endamoeba Leidy, 1879, or Entamoeba Cassagrandi and Barbagallo, 1895, and for using the species name *histolytica* Schaudinn, 1903, or *dysenteriae* Councilman and Lafleur, 1891 Another controversial point is whether the species designation *williamsi* or *butschlii* is to be preferred for amebae of the genus Iodamoeba

Endamoeba Histolytica (Schaudinn, 1903)

E histolytica is a protozoan which varies in size from 10 to 30 microns, most commonly occurring in the lower range The trophozoite moves actively, constantly changing shape In fresh and vigorous specimens the body is frequently elongated, with but one large pseudopodium projecting in the direction of movement A similar shape may also be observed in organisms in permanent mounts In the usual preparations, however, the rounded forms predominate, if the sample has stood for some time after collection before being examined.

One of the most noticeable morphologic characteristics of these protozoa, when they are alive, is the ease with which the ectoplasm can be distinguished from the endoplasm The ectoplasm is hyaline and transparent, while the endoplasm is translucent and more granular In the endoplasm can be seen vacuoles which may contain ingested red blood cells, although many do not show these corpuscles There is no food material within the endoplasm In degenerated specimens, vacuoles containing bacteria and other extraneous particles can be seen This also occurs in cultures, in which also starch granules are ingested

The nucleus is spherical, vesicular in type, with a series of small peripheral, refractile, quite regular lines of granules There is a very refractile central karyosome In preparations stained with hematoxylin, the peripheral chromatin granules are regular in shape and of uniform size, between the granules and the small central karyosome there is a series of small radiations of chromatin granules of variable staining intensity

The so called precystic forms are round and devoid of pseudopodia or nutritional inclusions A cyst wall is lacking

Cysts, usually spherical or spheroidal, are of variable size, measuring from 5 to 20 microns, averaging 10 microns It is thought that the cysts tend to be of uniform size within a certain race and that consequently there are different races of this species which differ from each other in the size of the cysts

The nucleus of the cyst has the same appearance as that of the trophozoite In newly formed cysts, only one nucleus is seen After division, this nucleus forms two, and by the second division, four nuclei This number is characteristic of mature cysts and predominates in specimens obtained from fecal matter

Bar like bodies, called chromatoid bodies, are frequently observed, they have rounded ends and appear very refractile in fresh specimens In preparations stained with iron hematoxylin, they are intensely black

Physiology—*E histolytica* is exclusively parasitic It must live within the body tissues of man or animals The trophozoites can survive for only a short period of time outside the body of the host The cysts have greater resistance

Like all parasites which inhabit the intestines, *E. histolytica* has become adapted to living in media poor in oxygen, but the organism is not a strict anaerobe since it can apparently be cultivated under aerobic conditions

Life Cycle—Mature or quadrinucleate cysts constitute the infective forms They enter the human organism by way of the mouth, passing undamaged through the stomach, thence to the small intestine Here the cyst wall softens and breaks, due to the action of digestive ferments, and a quadrinucleate ameba is released The quadrinucleate ameba

undergoes two cytoplasmic divisions without further nuclear division giving rise to four active amebae. Occasionally nuclear division may also take place; this results in the production of eight very small amebae (Faust 1943).

The metacystic amebae migrate into the large intestine and establish themselves in the walls, especially in the ileocecal region and in the first part of the ascending colon, as well as in the rectosigmoid. At these sites at autopsy there is seen a predominance of lesions caused by *E. histolytica*. The infection is very persistent, according to Dobell and Stevenson (1918); *it may last throughout the life of the host*.

While in the intestinal mucosa the amebae multiply repeatedly by binary fission (Dobell 1919). For reasons as yet unexplained some of the entamebae which remain in the intestine expel their nutritional material, undergo reduction in size, possibly by division, and become rounded, constituting the so-called *precystic forms*. These precystic *forms are later enveloped by a resistant membrane forming the uninucleate cysts*. When they mature they are transformed into the quadrinucleate infective forms. These forms, if ingested by the *proper host, begin again the life cycle just described*.

Although the habitual site of *E. histolytica* is the large intestine, at times the parasites are carried to other organs, where they produce suppurative abscesses.

Culture.—*E. histolytica* is easily cultivated on various media, the most commonly used being those of Boeck and Drbohlav (1925), Locke egg serum or Locke egg albumin, Craig, St. John serum media, Tsuchiya (1934), and Balamuth.

Inoculation of Animals.—Lösch, who discovered *E. histolytica*, successfully reproduced *the infection in dogs, and this method, though little favor, has come into usage again*, especially by Faust (1930). Kittens were used for the first time by Hlava in 1887; they are considered excellent laboratory animals for this purpose and are now used extensively. Jones (1946) introduced the use of rats in such experiments.

Endamoeba Coli (Grassi 1879)

E. coli is somewhat similar to *E. histolytica*. It is usually described as being larger, varying from 10 to 40 microns.

The ectoplasm is much less hyaline and less transparent than that of *E. histolytica* and is not well differentiated *from the endoplasm. In the endoplasm there are a large number of* vacuoles containing a variety of nutritional materials—bacteria, yeasts, *cysts of other* protozoa, etc. The pseudopodia are similar in shape to those of *E. histolytica* but frequently are blunt and are not projected in any definite direction.

The nucleus is characterized by peripheral chromatin granules, coarser and more irregular than those of *E. histolytica*. They are more readily distinguishable due to their refractile character. The karyosome, which is larger and less refractile, is excentrically located.

Precystic *forms*, which measure about 15 microns, are similar to those of *E. histolytica*, from which they can be differentiated by nuclear characteristics.

The **cysts** are spherical or spheroidal, seldom irregular, and vary from 10 to 30 microns. The membrane which surrounds them presents a well-marked double contour. They are *originally uninucleate, though soon they become binucleate, then four and eight nuclei, the* last number considered typical of mature cysts. They contain a large amount of glycogen, which accounts for their dark brown color with iodine solution. They frequently lack chromatoid bodies; when present they are needle-shaped and sometimes joined together, forming larger or smaller clusters.

Life Cycle.—The life cycle is similar to that of *E. histolytica*, with the difference that this ameba, once established in the large intestine, lives within the lumen and feeds on bacteria and other material without invading the tissue. For this reason it is considered a simple commensal.

The incidence is high. It has been calculated that about 50 per cent of the entire population of the world harbors *E. coli*. The mechanism of transmission is presumably the same as that for *E. histolytica*.

This species is difficult to cultivate. The parasite is not easily transmitted to animals.

There is also another noteworthy discrepancy with respect to the correct designation of species, the discussion centering principally upon the justification for using the generic name Endamoeba Leidy, 1879, or Entamoeba Cassagrandi and Barbagallo, 1895, and for using the species name *histolytica* Schaudinn, 1903, or *dysenteriae* Councilman and Lafleur, 1891 Another controversial point is whether the species designation *williamsi* or *bütschlii* is to be preferred for amebae of the genus Iodamoeba

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undergoes t o cytoplasm d v sions without further nu lear d v s on g v ng rise to four active amebae Occas onally nuclear d v s on may al o take place th s results in the pro du t on of e gl t very small amebae (Faust 1943)

The meta ystic amebae m grate into the large inte t ne an l establ sl themselves in the walls espec ally in the ileocecal reg on an l in the first part of the as en l ng colon as well as in the rectos gmo d At these s tes at autopsy there is seen a pre lom nance of les ons caused by *E histolyt ca* The infect on s very pers tent ac or l ng to Dobell and Stevenson (1918) it may last throughout the l fe of the host

Wl le in the intest nal mucosa the amebae mult ply repeatedly l y b nary fi s on (Dobell 1919) For reasons as yet unexpla ned some of the e amebae wh ch rema n in the intest ne exp l the r nutr t onal mater al un l rgo re luct on n s ze poss bly l y l v on an l become roun led const tuting the so called *precyst c* forms These pr cyst c forms are later en v loped by a res stant membr ne form ng tl e un nu leate cysts When they mature they are transformed into the quadr nucleate nfect ve forms Tl e e forms if inge te l by the proper host begin aga n the l fe cycle just de cr bed

Although tl e l ab tual s te of *E h stolyt ca* is tl e large nte t ne at t n es the parasites are carr ed to other organs here tl ey produce sup purat ve abscesses

Culture—*E h stolyt ca* is eas ly cult vated on v r o s me l a the most commonly used be ng tl ose of Boeck an l Drbohlav (19 5) Locke egg serum or Locke egg alb im n Cra g St John serum me l a Tsuch ya (1934) and Balamuth

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The ectoplasm s n u h l s hyal ne and transpar nt than th t of *E histolyt a* and is not well d fferent ated from the en lopla m In tl e en loplasm tl re are a large number of vacuoles conta n ng a var ety of nutr t o al mater als—bacter a yeast cy ts of other protozoa etc The pseu l po l a are s m lar in sl ape t those of *E h stolyt ca* but frequently are blunt an l are not project l n any l fin te d r ct o

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Precystic forms v h cl n ea re al out 20 m crons are s n lar to tl ose of *E h stolyt ca* from wh h tl ey can l e l fferent ated l y nuclear chara ter t s

The **cysts** are spher al or sp ro lal s llon rregular an l vary from 10 to 30 m crons The membrane h h surro n ls tl em presents a ell marked doul le contour They are orig nally u nu leate thr ugl su ce ve l s o tl ey form two four and e ght nucle the la t number co lered typ al of mature cy ts They conta n a large amount of glycogen wh h ac ounts f r tl e r d rk l r n col r l en t nged tl odine They frequently lack chromato l lo l es l en present they are nee ll sl pe l an l s n et mes jo ned together form ing larger or smaller clu ters

Life Cycle—The l fe c cle s s m lar to that of *E h t lyt ca* w th tl e l fference that th s ameba once estal l shel n the large intest ne l es w th n the lumen an l fee ls on bacteria an l otl er mater al w thout invad ng tl e t s e For tl s reason it is cons lered a s mpl commensal

The **incidence** s h gh It has been cal late l that al t l per cent of the ent re populat on f tl e w rll harbors *E o* Tl e m lan m f tran m on is supposedly the same as that f r *E h st yt a*

This spec es s d ff ult t cult vate The para te is not eas ly transm tted to an mals

Differentiation Between Endamoeba Histolytica and Endamoeba Coli

Since *E histolytica* and *E coli present major points of similarity, and since* it is important to identify *E histolytica* correctly, the most important characteristics generally used to differentiate these two amebae are given

The cysts and trophozoites of E histolytica are usually smaller than those of *E coli* Size alone however is not an absolute means of differentiation, since at times the sizes vary and cysts and trophozoites of *E histolytica* are rather large

One of the most important means of identification is the differentiation of the ectoplasm and the endoplasm and the nature of the amebic movements, this is of value, however, only in normal and vigorous living specimens

The contents of the food vacuoles is very important: *E histolytica habitually shows only ingested erythrocytes, or completely lacks food vacuoles,* whereas *E coli* shows very abundant *food* vacuoles containing a variety of material In *degenerated E histolytica* are seen vacuoles containing ingested *bacteria and there are some reported cases of E coli containing ingested erythrocytes* (Tyzzer and Geiman 1938)

Cysts help differentiate the two species the size, the nature of the membrane (single in *E histolytica,* double in *E coli*), and the nature of the chromatoid bodies Of greater importance is the structure of the nuclei which, as in the trophozoites offers a more certain identification in stained slides The number of nuclei is also a means of differentiation but *this is not always reliable It appears* (Beltran, 1945b) that even though the number of supernucleated cysts of *E coli* may be large up to 20 per cent this is of no particular importance in diagnosis, whereas the number of supernucleated cysts in *E histolytica,* which might cause serious confusion is barely 3 to 4 per cent



Fig 8—Trophozoite of *Endamoeba gingivalis* stained with iron hematoxylin The nucleus is seen in the central portion the remnants of ingested leucocytes in the food vacuoles (×3 000) (Original photomicrograph of E Beltrán)

Endamoeba Gingivalis (Gros, 1849)

E gingivalis, although not a true intestinal ameba, since it lives in the mouth, is mentioned here only because of its high incidence it occurs in about

50 per cent of adults Morphologically it resembles *E. histolytica* from which it differs in a few slight details of nuclear structure The food vacuoles contain a variety of materials, such as bacteria and other microorganisms and the remnants of leucocytes

This species has no cystic form in its life cycle It is assumed that transmission from person to person takes place by direct contact, especially through kissing

This species has aroused the interest of many authors Some (Bass and Johns, 1915, Smith and Barrett, 1915, etc) considered it to be of etiologic importance in pyorrhea alveolaris, although most contemporary authors do not accept this view In accordance with our own investigations (Beltrán and Molina 1944), we think that this subject still merits further serious consideration before it will be possible to arrive at a definite conclusion

Endolimax Nana (Wenyon and O'Connor 1917)

These are small amebae varying from 6 to 12 microns Differentiation between the ectoplasm and the endoplasm is variable while perfectly marked in some in others it is observed only with the greatest difficulty or not at all The endoplasm contains abundant food vacuoles containing a variety of material This fact in conjunction with the characteristics of their movements sluggish and in different directions sometimes causes this species to be confused with small *E. coli* The nucleus constitutes the most important diagnostic characteristic of the parasite

Cysts are ovoid less frequently spherical with four nuclei in the mature state The nuclei have the same characteristics as those found in the trophozoite, but they are barely visible in fresh specimens

They measure approximately 8 to 10 microns along the longer axis Young stages frequently show glycogen distributed diffusely or concentrated in vacuoles which sometimes resemble those found in Iodamoeba

Dobell (1919) described the occasional presence of filaments which stain black with iron hematoxylin

The life cycle of this species appears to be similar to that of *E. coli* being a simple commensal of the human intestine

Incidence is about 10 per cent In our investigations in Mexico we found an incidence between 8 and 32 per cent

Iodamoeba Williamsi (Prowazek 1911)

These are small organisms varying from 5 to 20 microns The ectoplasm is not clearly differentiated from the endoplasm The endoplasm contains numerous nutritional vacuoles with the most varied contents Movement of the ameba is sluggish frequently not directional

The nucleus which is practically invisible in fresh specimens is the principal distinctive characteristic of these amebae in stained preparations

Cysts are most frequently uninucleate The nucleus is practically invisible in fresh specimens and barely detectable in preparations treated with iodine The most notable characteristic is the great irregularity of outline Another very characteristic structure is the glycogen vacuole with its definitely limited outline which occupies a large part of the cyst In fresh specimens or in specimens stained with hematoxylin it appears as a clear space while in specimens stained with iodine it appears as a well defined mahogany-colored mass

It has often been stated in the literature that the cysts are found in large numbers in infections due to this species but that only rarely are the trophozoite forms found. It has

been my experience (Beltrán, 1945a) that this is not necessarily the case, since the vegetative forms, sufficiently abundant in liquid feces, also are found in appreciable numbers in formed stools.

The life cycle is similar to that of the species just described, and it is also considered as harmless to man. It occurs quite frequently, our studies showing an incidence of 7 to 31 per cent.

Dientamoeba Fragilis (Jepps and Dobell, 1918)

These parasites are easily destroyed, for which reason the name *fragilis* has been given to the species. They are small, from 4 to 12 microns. The ectoplasm and endoplasm are clearly differentiated. They project hyaline, transparent pseudopodia which resemble those of *E. histolytica*, although they are not formed with the same rapidity. The nucleus is the most outstanding characteristic. There are often two nuclei.

The life cycle differs from other parasitic amebae of man, with the exception of *E. gingivalis*, in that no cysts are known. Because of this, details of the transmission are still obscure.

Reports of the incidence of this parasite vary. Most authors agree that it is the least frequent of the amebae of man. In our own epidemiologic surveys (Beltrán and Larenas, 1941), we have found an incidence as high as 9 per cent.

Although the majority of authors believe that this organism is not pathogenic to man, there are several reports of clinical cases supposedly caused by this species. Recently Wenrich (1944) reviewed the literature on this point and insisted upon the possible pathogenicity of these organisms although he admits that data sufficient for absolute confirmation have not been brought forth.

MASTIGOPHORA

Members of this class are characterized by having, as organs of locomotion, long vibratory whip-like appendages, called flagella, from which is derived the name "flagellates," commonly applied to them.

Certain flagellates live in the blood and the tissues; these are called *hemoflagellates*. Another group lives in the intestine; these are called *intestinal flagellates*. Generally included in this group, although they are not, strictly speaking, intestinal inhabitants, are species found in the mouth and in the vagina.

Polymastigina, one of the four orders into which this class is divided, is characterized by three to eight flagella, with the exception of the family Polymonadinae, which has more. In some species, there is an undulating membrane. They have one or more nuclei of the vesicular type. Certain forms which feed upon solid particles have a cytostome for ingestion, while others lack such orifices and derive their nourishment by absorbing nutritive materials through the entire body surface. Some form both trophozoites and cysts, while others have no cystic stage. There are a great number of species of both free-living and parasitic forms.

Several species live in man. Most authors agree that the following are parasitic to man: *Trichomonas hominis* (Davaine, 1860), *Trichomonas tenax* (O. F. Muller, 1773), *Trichomonas vaginalis* Donné, 1837, *Giardia lamblia* Stiles, 1915, *Chilomastix mesnili* (Wenyon, 1910), *Enteromonas hominis* da Fonseca, 1915, *Retortamonas (Embadomonas) intestinalis* (Wenyon and O'Connor, 1917).

Other species have been described, unsupported by sufficient evidence, and not accepted by the majority of authors.

There is also a great discrepancy with regard to the nomenclature of these parasites

Genus Trichomonas

These are pear shaped organisms with rounded anterior end The body is *traversed throughout the long axis by an axostyle which projects from the* posterior end, *according to the species* The flagellar apparatus consists of free flagella at the anterior end with one flagellum extending *from front to* back to form the axoneme of the undulating membrane

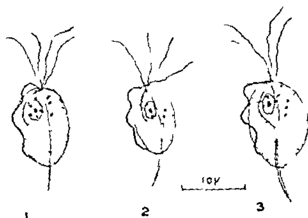


Fig 9—Comparative diagram of human parasites in the genus Trichomonas 1 *T hominis* 2 *T buccalis* 3 *T vaginalis* (Original drawing of T G de Beltrán.)

Trichomonas Hominis Davaine 1860

T hominis varies in length from [illegible] to 20 microns Each anterior flagellum originates from an independent basal corpuscle Close to this is the flagellum which forms the axoneme The axostyle is straight or slightly curved and extends beyond the posterior extremity The cytostome is small buttonhole in shape and is found near the anterior end Near the anterior extremity is the nucleus which is spherical or slightly ovoid, with a small karyosome, with a variable quantity *of* chromatin granules in the *nuclear* material In the anterior part of the body between the wall and the *nucleus* there is a group of small blepharoplasts, in longitudinal rows giving a "dotted" effect.

Old, degenerated organisms have an ameboid appearance with few structural details In such cases the most apparent characteristic is the undulating membrane, movements of which usually persist for a long time

The parasite moves rapidly by a series of small "jumps", the undulating membrane moves continuously This movement under low magnification appears merely to be a change in the shape of the body The anterior flagella also vibrate rapidly

They obtain their nourishment by ingesting various microorganisms Occasional ingestion of red blood cells has been observed (Hegner 1938)

Reproduction occurs by longitudinal binary fission There are no cysts the supposition being that transmission from subject to subject is accomplished through trophozoites which can pass through the stomach without damage

Some investigators consider Trichomonas nonpathogenic, others believe they can produce diarrhea and colitis Among those who take the latter view are Escomel (19[illegible]7) Kofoid and Swezy (1924) and Muro (1937)

Some authors relate the problem of pathogenicity to the number of flagella that is they consider that *only those with five flagella* (the genus Pentatrichomonas) are pathogenic

Incidence is variable In our investigations this parasite was found in 9 to 54 per cent

Culture of *T hominis* is successful in media similar to those used for *E histolytica* Rats can be easily infected with *T hominis* but the susceptibility of different strains of rats varies (Hegner and Eskridge, 1935)

Trichomonas Tenax (*Muller 1773*)

This flagellate is found in the human mouth in the tartar around the teeth *and in the cavities* of dental caries and in the pus of pyorrhea alveolaris (Gradwohl and Kouri 1948)

The morphology is similar to that of *T hominis* Whether or not they are the same species has been much discussed Wenrich (1931 1939) found certain morphologic differences which may be seen in Fig 9 Experiments by Bonestell (1936) and others confirm that we are dealing with distinct species

The *incidence of this parasite appears to be rather high* since Beatman (1933) found 22 7 per cent positive cases in 350 persons examined in Philadelphia It is supposed that transmission occurs in a manner similar to that of *E gingivalis*

Trichomonas Vaginalis Donné, 1837

This species shows great morphologic similarity to the preceding species, however *some differences which can be seen in Fig 9 may be observed*

It occurs in the vaginal mucus and reproduces by longitudinal binary fission Formation of cysts has not been observed Its nutritional requirements are still in dispute, some authors assume that it lives upon bacteria or that it ingests red blood cells (Andrews 1929) Others (Bland et al 1932) believe that leucocytes are ingested by Trichomonas and in turn that Trichomonas are ingested by leucocytes

Transmission is venereal as well as by contact with contaminated objects

Although the pathogenicity of this organism is still a matter for discussion most authors hold *it responsible for certain gynecologic conditions*

Incidence appears to be high in both sexes Andrews (1938) found an infection rate of 38 per cent Bland et al (1932) of 17 8 per cent in women Deo (1944) found 15 5 per cent of males infected He believes that the male is the transmitter and the female the reservoir

Cultivation of *these organisms is successful in many media* containing physiologic saline and protein material

Giardia Lamblia Stiles 1915

The body the major axis *of which is approximately* 10 to 20 microns is pear shaped with the wider part at the anterior end tapering to a point toward the posterior end From the posterior extremity project two tail like flagella *If viewed from the side the organisms*

have a concave structure, like a sucker, at the anterior extremity this is the *cytostome* and serves to attach the parasite to the wall of the small intestine, producing irritation of the intestine

The organism is seen in Fig 10, with a large cytostomal area, peristomal fiber surrounding the two nuclei, forming a sort of bowknot, and a series of blepharoplasts from which flagella arise The latter are two anterior, two lateral two ventral and two caudal Toward the center of the body are two wedge like parabasal bodies

The cysts are ovoid, from 10 to 15 microns along the greater axis, with thick, resistant walls The shape of these cysts is very characteristic Within the cysts, two to four anterior nuclei and remnants of the fibers which form the axostyle are seen Frequently the parabasal bodies are observed

In fresh stools these organisms may be seen moving rapidly, with their flagella, which are more readily visible than those of other species

Infection occurs by ingestion of cysts which pass through the stomach and reach the small intestine

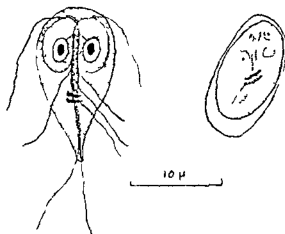


Fig 10—Diagrammatic representation of *Giardia lamblia* At the left is a trophozoite at the right, a cyst (Original drawing by T G de Beltrán)

Some authors deny a pathogenic role others insist upon it There are reasons for assuming that it is pathogenic

This parasite is cosmopolitan although more common in high temperate regions We have found an incidence of 6 to 34 per cent

Chilomastix Mesnili (Wenyon 1910)

This organism measures 10 to 20 microns along its longer axis It also is pear shaped but is not bilaterally symmetrical

The posterior half of the body is often twisted It has a single nucleus relatively large and vesicular near the anterior extremity Near the nucleus there is a group of blepharoplasts from which arise three free anterior flagella Another flagellum with the same origin passes within the organism inside the cytostome the sides of which are supported by two small lateral fibrils

The cysts are lemon shaped 6 to 9 microns long The nucleus as well as remnants of the neuromotor apparatus especially the flagellum within the cytostome can be seen

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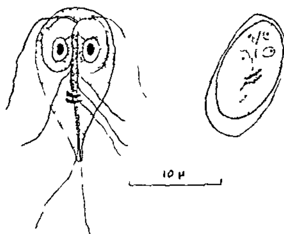


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The cysts are lemon shaped, 6 to 9 microns long The nucleus, as well as remnants of the neuromotor apparatus, especially the flagellum within the cytostome, can be seen

These organisms inhabit the large intestine where they feed on bacteria and other minute particles Most authors do not believe that they play a pathogenic role The cysts appear to be exclusively a form of protection (Geiman 1935)

The incidence of C mesnili varies in different localities our investigations showing them as ranging from 10 to 25 per cent

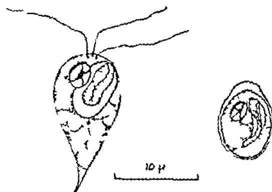


Fig 11 —Diagrammatic representation of Chilomastix mesnili At the left is a trophozoite at the right a cyst. (Original drawing by T C de Beltrán)

Enteromonas Hominis da Fonseca 1915

This is one of the smallest of intestinal flagellates of man measuring 4 to 8 microns They are of various shapes

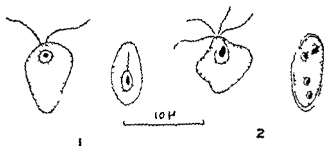


Fig 12 —Schematic representation of trophozoite and cyst of Retortamonas intestinalis, 1 and Enteromonas hominis 2 (Original drawing by T C de Beltrán.)

They have a single nucleus in the anterior extremity adjacent to a group of blepharoplasts from which originate the free flagella as well as another flagellum which extends along the length of the body without however forming an undulating membrane

The cysts are elongated from 6 to 8 microns long and present from one to four nuclei according to the stage of maturity

Little is known of their physiology and life cycle They are considered harmless in their relationship to man *Incidence is relatively low* in Mexico we have found 4 per cent

Retortamonas (Embadomonas) Intestinalis (Wenyon and O Connor 1917)

These flagellates are small 5 to 6 microns The parasite presents the form of a truncated cone with the flat extremity corresponding to the *cytostome*

in the anterior part It has a vesicular nucleus near the anterior extremity and two free flagella of unequal size

Cysts measure 4 to 6 microns and resemble those of *C mesnili*

This parasite seems to be harmless Incidence in our investigations never exceeded 3 per cent

INFUSORIA

These forms are characterized by vibratory locomotor appendages called cilia, which may partially or entirely cover the body and which at times combine to form composite organs of locomotion such as *membranellae* and *cirri*

The nuclear apparatus is composed of two distinct elements the *micronucleus* and the *macronucleus*, the first having a sexual function

A great number are parasitic Some forms such as *Ichthiophthirius multifilus* which parasitize the skin of certain fish may be important from the human point of view

One or more species of the genus Nyctotherus has been cited in man, but such references are now considered erroneous (Watchermann, 1938, Beltran, 1939) We recognize at this time but one infusorial parasite of man *Balantidium coli*

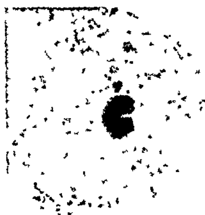


Fig 13 —Trophozoite of *Balantidium coli*, stained with Delafield hematoxylin Note the macronucleus in the center (X3 000) (Original photomicrograph of E Beltrán)

Balantidium Coli Malmsten 1857

This organism is ovoid and slightly tapered at the anterior end where a subterminal peristome is found It varies greatly in size, according to Hegner (1930) from 30 to 200 microns although the average size is 45 by 60 microns The cilia are arranged in longitudinal parallel lines around the body They are uniform except at the anterior extremity, where they become longer

The macronucleus situated near the central part of the body is usually reniform A small spherical *micronucleus* is found in its immediate vicinity There are two spherical contractile vacuoles situated laterally In the posterior portion there is a cytoproct or cytopyge subterminal and oblique Numerous food vacuoles may be observed, filled with bacteria and other material

Cysts, spherical and subspherical are about 50 microns in diameter, with a thick membrane with double contour Within the cyst there is a rounded mass of cytoplasm containing the nucleus

There is no agreement as to the details of the life cycle

B coli causes a severe form of dysentery The incidence is low Young (1937) reported that in the United States scarcely forty three cases of this infection are known to date and in Mexico (Beltran 1942) we found only sixty three although later more cases were recorded

Swine and various species of monkeys are often parasitized by *B coli*

SPOROZOA

These animals form a class represented exclusively by species that are parasitic

The only species which inhabits the human intestine is *Isospora hominis*, of the order Coccidia which parasitizes the epithelium of the digestive tract and its glands Members of this order usually present alternating generations with sexual and asexual phases which usually occur in the same host The infective forms are the spores which are resistant to external environmental conditions because of their protecting coverings

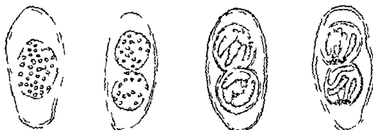


Fig 14 —Diagrammatic representation of successive stages in the development of the oöcysts of *Isospora hominis* (X3 000) (Original drawing by T G de Beltrán)



Fig 15 —Oöcyst of *Isospora hominis* immature (unstained specimen) (X3 000) (Original photomicrograph of I Beltrán)

Isospora Hominis Fantham 1917

Only their oocysts have been found the other stages of the life cycle being unknown *They are elongated with an ovoid contour frequently with* one of the extremities bottle neck shaped about 29 by 13 microns The sporocysts are formed within them with average dimensions of 12 microns, in these are observed when they mature four elongated sporozoites

Infection by this parasite appears to be rare Magath (1934) found in the literature only some 200 known cases In Mexico the first case was found recently (Beltran and Larenas 1944) Other cases were found later as yet unpublished

Little is known of its relationship to the host Most authors believe that it is pathogenic

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CHAPTER 4

AMEBIC DYSENTERY, HEPATIC ABSCESS AND OTHER INTESTINAL CONDITIONS CAUSED BY PROTOZOA

Oscar Felsenfeld and Viola Mae Young

AMEBIASIS

DEFINITION

Amebiasis is the proper designation for invasion of the body by *Endamoeba histolytica*. In medical circles this term is rapidly replacing the obsolete "amebic dysentery," which is now applied only to that dysenteric syndrome which characterizes severe amebic ulcerative colitis. The use of the term "amebiasis" is substantiated by the necessity of including amebic abscess, subclinical conditions, and mild disease under the same heading as more serious illnesses caused by the same organism. Many writers have felt that neither the "symptomless" carrier state, nor certain cases in which the liver affection is of primary interest without apparent dysenteric symptoms or even diarrhea should be called "amebic dysentery." Thus the term "amebiasis" has been coined and accepted.

AGENT

Most authorities consider *E. histolytica* as the only pathogenic intestinal ameba. The morphology and life cycle of the ameba are described in Chapter 3. It must be emphasized here also that only the cysts of this organism are infective. The trophozoites are easily destroyed. Cysts, however, are able to remain alive for as long as three weeks in the feces. While boiling destroys cysts in a few seconds and temperatures of 6[illegible] to [illegible]0° C. are not resisted for five minutes, some cysts are able to survive at [illegible] to 4° C. for months. Chemical disinfectants do not destroy amebic cysts as quickly and reliably as they react on bacteria. Chlorine, for example, in a concentration of four parts per million parts of water must act for thirty minutes in order to destroy cysts. This action depends upon the temperature and the hydrogen ion concentration.

Not all strains of *E. histolytica* are equally resistant and virulent. Considerable work on the virulence of amebae was performed by Meleney and Frye (1933, 1936, 193[illegible], 1941) and Faust et al. ([illegible]). It may be stated that the pathogenicity of amebic strains varies considerably, those from [illegible] [illegible] generally being less virulent. There is also [illegible] [illegible] [illegible] of the amebae. The so-called "small form" or "small type" of *E. histolytica* was studied by Dobell ([illegible]), Andrews ([illegible]), Sapero et al. (194[illegible]), Frye and Meleney (1939) and others. Brumpt (193[illegible]) called it *Endamoeba dispar* and does not believe in its pathogenicity. [illegible] Young (1944) and Felsenfeld (1945) studied the "small type" in the midwestern United States. The cysts of this type are less than 10 microns in diameter. The trophozoites contain red blood cells only exceptionally. This variety is either only slightly pathogenic or nonpathogenic for cats and dogs. It causes only mild amebiasis. Later complications and intestinal perforation have never been observed in such infections. It disappears promptly after treatment with [illegible] preparations. In unstained preparations or in preparations stained with [illegible] it is easily mistaken for *Endolimax nana*.

TRANSMISSION

Patients with acute cases of *typical amebiasis, where only trophozoites* are excreted, do not transmit the disease as a rule. The real sources of infection are "symptomless carriers" or "symptomless cyst passers" and persons suffering from vague intestinal complaints which in a temperate climate may be mistakenly diagnosed as "*spastic colitis*," "*idiopathic* constipation," or "food allergy" and, therefore, are not being treated. Such persons, when working as food handlers, may cause many cases of amebiasis if viable cysts are harbored under their nails or carried on their soiled hands. In many tropical and subtropical countries where amebiasis is endemic, most of the food handlers have been found to be infected when surveys were made to detect the frequency of amebiasis.

In the Near East and in China, as well as in many other countries, mainly in the tropics, night soil is used as fertilizer. Vegetables grown under such conditions may be heavily contaminated with cysts and are a constant source of infection. Before marketing, vegetables are "freshened" by dipping into sewage. They become contaminated with cysts and serve *to spread amebiasis*.

Flies and other insects, such as cockroaches, often come in contact with fecal material and may mechanically transmit the infection with their legs or mouth parts. Flies, moreover, actually breed in feces. *If they swallow fecal material containing amebic cysts, they may* excrete such cysts for as long as three days. Insects carrying cysts often transfer the organisms to food, which, when consumed by susceptible persons, may cause infection.

Water is a frequent source of amebiasis. Its importance in the epidemiology of amebiasis was first recognized by Manson (1925) on Cape Verde, where he traced the infection to a well. Springs, unprotected wells, cisterns, and streams may contain contaminated water. Amebic cysts may be introduced into such sources of drinking water from seepage of sewage and by the use of contaminated drinking buckets or from infected persons swimming or washing in water which flows into such drinking water. The classical example of a water borne outbreak is that which occurred in Chicago during the Century of Progress Exposition. According to the committee report (1936), over 1,400 persons developed amebiasis, with about 100 deaths. The cause of the contamination of the water was a cross-connection between sewage and drinking water pipes in two large Chicago hotels.

Age seems to play a certain role in amebiasis. Faust (1942) and Craig (1944) stated that children have less opportunity and less time to acquire the infection. Ivanhoe (1943) studied the transmission of amebiasis in a home for children. This examination showed that under conditions favorable for the spread of the infection, that is, poor hygiene, crowding, etc., epidemiology in children does not differ from that in adults. Costa Mascaró (1945), Castelli (1944) and Tupas et al. (1946) found many cases of amebiasis in children and also in nurslings. In the observations of the senior author (1947) the youngest child with amebiasis was 16 days old; *this child had contracted his infection from a "cyst passer" grand*mother. The majority of patients however, are in the age group between 20 and 40 years.

Sex seems to be important; men are more often infected than women. This may, perhaps, be related to their occupations and hobbies, which lead them into situations where infection is more easily acquired (Manson Bahr, 1945).

Race is not a significant factor. Indigenous inhabitants, however, seem to suffer less from complications in highly endemic zones because they have developed partial immunity during earlier infections.

Seasonal incidence is observed because there are more flies during the warmer seasons, and, consequently, a greater number of mechanical transmissions occur. On the other hand, the rainy season in the tropics causes floods which rapidly spread infected feces over a wide area. Many exacerbations are observed after holidays and feasts, when individuals are apt to overeat, thus causing a relapse of the amebiasis.

The incidence of amebiasis was analyzed by Manson Bahr (1943), Craig (1944), Morton (1946), Cintra do Prado and Figliolini (1946), Klatskin (1946), Tallant and Maisel (1946), Elson et al. (1947), Felsenfeld and Young (1946 and 1948), and others. Craig (1944) gave

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Wenrich and Arnett (1942)—12 per cent of food handlers and 10 7 per cent of student assistants in a Philadelphia school

Headlee and Calle (1942)—5 per cent among students in a Kentucky rural college

Nickel (1942)—4 4 per cent of the general population of Mississippi

Summers (1942)—4 per cent of the students in a Florida school

Browne et al (1945)—14 1 per cent among gastrointestinal patients in the New Orleans area.

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Incidence in state hospitals and other mental institutions seems to be high, mainly among the personnel working with amebic patients according to Burrows (1943) and Hopp (1944) The principal reason for the high infection rate, however, is the lowered hygienic habits of mental patients, the overcrowding and the generally poor living conditions in many mental hospitals Birnkraut et al (1945) found 11 5 per cent amebic infection in an asylum While 6 per cent of the employee food handlers harbored *E histolytica* 14 per cent of the patient food handlers were infected Castelli (1944), however, called attention to the fact that amebiasis is increasing not only among people living under bad hygienic conditions, but also among the rich and well to do

In South America former investigations revealed that 6 to 85 per cent of the population were infected with *E histolytica* Tropical regions are most heavily infested Beltrán (1942, 1944) and Beltrán and Larenas (1941, 1943) have shown that in Mexico the frequency of amebiasis varies from 7 to 47 per cent or higher according to locality and hygienic conditions. Ravelo Barré and Thomen (1943) found 14 per cent infestation in the Dominican Republic In Brazil Renault and Versiani (1940) do Amaral (1943) and Vello de Silva and Lopes Fontes (1944) reported a varying percent of the population infected, 8 33 to 40 per cent

In Europe, 1 to 10 per cent of the population are infected In Asia, the most heavily infested areas are in the south—Bengal, Bombay, and South China, respectively Many cases have been reported from North Africa fewer from tropical and South Africa Amebiasis is not often found among the inhabitants of Australia

PATHOLOGY

Endamoeba histolytica lives in the tissue of the intestinal wall which it penetrates with the aid of proteolytic ferments (called *cytolysins* by their discoverer, Craig) and by motility Those which do not enter the intestinal wall are discharged with the feces Faust (1941) offered conclusive proof that *E histolytica* cannot live in the lumen of the intestines and also that small lesions are found in the "cyst passers" who do not show symptoms of amebiasis Such lesions consisting of microscopic areas of cytolysis and superficial necrosis, are very often overlooked In order to be observed they must be carefully searched for by the pathologist Thus one should not use the expression "carrier" in amebiasis, because lesions are always present when cysts occur in the stools.

The invading amebae destroy the columnar epithelium of the large intestine and dig down into the crypts of Lieberkühn Finally they penetrate the basement membrane of the mucosa and enter the submucosa They engulf blood cells and remnants of tissue cells Cysts are never found in the tissues—only trophozoites

The microscopic picture of the lesions reveals stasis and capillary thrombosis, resulting in edema and necrosis Later, fibrosis may develop in the

TRANSMISSION

Patients with acute cases of typical amebiasis, where only trophozoites are excreted, do *not transmit the disease as a rule*. The real sources of infection are "symptomless carriers" or "symptomless cyst passers" and persons suffering from vague intestinal complaints which in a temperate climate may be mistakenly diagnosed as "spastic colitis," "idiopathic constipation," or "food allergy" and, therefore, are not being treated. Such persons, when working as food handlers, may cause many cases of amebiasis if viable cysts are harbored under their nails or carried on their soiled hands. In many tropical and subtropical countries where amebiasis is endemic, most of the food handlers have been found to be infected when surveys were made to detect the frequency of amebiasis.

In the Near East and in China, as well as in many other countries mainly in the tropics, night soil is used as fertilizer. Vegetables grown under such conditions may be heavily contaminated with cysts and are a constant source of infection. Before marketing, vegetables are "freshened" by dipping into sewage. They become contaminated with cysts and serve to spread amebiasis.

Flies and other insects, such as cockroaches, often come in contact with fecal material and may mechanically transmit the infection with their legs or mouth parts. Flies, moreover, actually breed in feces. If they swallow fecal material containing amebic cysts, they may excrete such cysts for as long as three days. Insects carrying cysts often transfer the organisms to food, which, when consumed by susceptible persons, may cause infection.

Water is a frequent source of amebiasis. Its importance in the epidemiology of amebiasis was first recognized by Manson (1925) on Cape Verde, where he traced the infection to a well. Springs, unprotected wells, cisterns, and streams may contain contaminated water. Amebic cysts may be introduced into such sources of drinking water from seepage of sewage and by the use of contaminated drinking buckets or from infected persons swimming or washing in water which flows into such drinking water. The classical example of a water borne outbreak is that which occurred in Chicago during the Century of Progress Exposition. According to the committee report (1936), over 1,400 persons developed amebiasis, with about 100 deaths. The cause of the contamination of the water was a cross connection between sewage and drinking water pipes in two large Chicago hotels.

Age seems to play a certain role in amebiasis. Faust (1942) and Craig (1944) stated that children have less opportunity and less time to acquire the infection. Ivanhoe (1943) studied the transmission of amebiasis in a home for children. This examination showed that under conditions favorable for the spread of the infection, that is, poor hygiene, crowding, etc., epidemiology in children does not differ from that in adults. Costa Mascaró (1945), Castelli (1944) and Tupas et al. (1946) found many cases of amebiasis in children and also in nurslings. In the observations of the senior author (1947) the youngest child with amebiasis was 16 days old; this child had contracted his infection from a "cyst passer" grandmother. The majority of patients, however, are in the age group between 20 and 40 years.

Sex seems to be important: men are more often infected than women. This may, perhaps, be related to their occupations and hobbies, which lead them into situations where infection is more easily acquired. (Manson Bahr, 1945.)

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vicinity In the beginning, when secondary bacterial infection is not present, leucocytes do not appear in the picture The amebae conglomerate near the edges of the ulcers, *in the crypts, and in the interglandular tissue* They often appear in "nests" *The amebae spread in the lymph spaces, in and along the thrombosed veins and capillaries, and gain access to the portal circulation, which carries them to the liver* This explains why the liver is the favored *site of amebic lesions*

The macroscopic picture is in agreement with this process *The first visible* lesions usually consist of yellow nodules localized mostly on the summits of the *mucosal folds* They contain viscid material, filling the cavity which has its

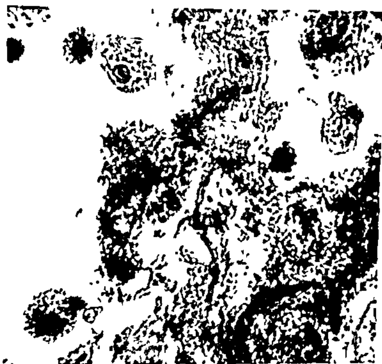


Fig 16 —Base of an amebic ulcer showing organisms (Original photomicrograph of Oscar Felsenfeld.)

base in the submucosa When such a lesion bursts into the lumen of the intestine, an ulcer, with undermined edges, narrow neck, and broad base, with a clean floor is formed This is the "flask shaped ulcer" When the ulcer spreads horizontally in the submucosa, a "buttonhole ulcer" *(bouton en chemise)* originates Small, superficial ulcers do not show inflammatory changes They are not undermined Many of them heal quickly and new ones are formed

Deep ulcers reach into the muscular layer They have thick, shaggy, swollen, much undermined, and elevated edges Fresh ulcers have rough and old ulcers clean bases There are numerous secondary hemorrhages, but

the mucosa between the ulcers has a grossly normal appearance Often sinuses are formed under the mucosa Sometimes the whole colon is covered with round ulcers, having raised undermined edges and white, fluffy bases These are known as 'sea anemone ulcers'

The entire colon may be covered with a dark exudate, the membrane may be undermined and burrowed This is called the 'seaweed colon.' Necrotic sloughs and remnants of more resistant supporting tissue on the base of deep ulcers are described as 'Dark hair sloughs' The intestine may resemble a buffalo skin



Fig 17 — Amebic liver abscess (Courtesy of Dr Paul B Szanto, Pathologist, Kankakee State Hospital)

Solitary isolated ulcers with hard margins which during life resemble malignant growths mainly when localized in the rectum are often found Amebic granuloma containing giant cells and amebae and resembling carcinoma is rarely observed

The walls of the intestine are often atrophic and dilated Even sacculation may occur between the ulcers Fibrosis mainly of the submucosa, leads to thickening of the intestinal wall Frequent combinations of atrophy and hyperplasia are observed

Secondary infections cause inflammatory changes The pathologic diagnosis of co existing bacillary and amebic dysentery may be very difficult *Anaerobic bacteria* mainly Clostridia so often abundant in the intestines may cause gangrene

Amebic ulcerations serve as a portal of entry for allergens which often cause allergic phenomena (Napier 1943 Klatskin 1946)

If the ulcers heal smooth depressed nonpigmented scars result The healing process includes formation of granulation tissue and rapid regeneration

Perforation of the ulcers occurs infrequently because of the protective hyperplastic proliferative reaction of the serosa of the intestines

According to Clark (1925) the lesions are most frequent and most extensive near the ileocecal valve in the flexures of the colon and in the rectum About 85 per cent of the patients show ulceration of the cecum and in about 60 per cent all parts of the lower bowel are affected About 20 per cent of the *patients do not have lesions in the rectum and sigmoid*



Fig 18 —Microscopic picture of liver abscess (Original photomicrograph of Oscar Felsenfeld)

The pathogenesis and pathologic physiology of the liver lesions have been minutely described by Manson Bahr (1943) They consist of foci of miliary necrosis or coalescent nonsuppurative areas, called liver abscess' Both may be solitary or multiple of variable size The liver abscess occurs most often in the right lobe and usually only one abscess develops No pyogenic membrane is found if the abscess is rapidly formed An old abscess has poorly defined connective tissue walls Charcot Leyden crystals hematoidin crystals fat globules cholesterol and remnants of tissue cells are found in the contents Amebae appear only in the living tissue The liver is enlarged Focal peritonitis and serous exudate are often seen Fatty degeneration and formation *of new bile channels are frequent*

The liver abscess may perforate into the abdominal pleural or pericardial cavities It may give rise to abscess formation in the lungs brain or other organs Skin lesions are rare and develop usually around amebic fistulae of the intestine Similarly urinary amebiasis is very unusual and originates most often following a perforation of the intestines or a perinephric or subphrenic amebic abscess into the kidneys or bladder (Watson, 1945)

CLINICAL SYMPTOMS

The *incubation time* is very irregular from a few days to several months

The clinical picture of amebiasis consists of many qualitatively and quantitatively different elements Several attempts have been made to classify the diverse clinical syndromes under which amebiasis presents itself Two of these classifications are most useful those of D'Antoni (1942) and Craig (1944) In the following pages the clinical picture of amebiasis will be discussed following closely D Antoni's division of the forms of this disease

One must realize that the clinical picture of amebiasis is governed not only by the actual extent of the pathology but also by a series of reflex and vasomotor changes induced by the lesions Triband (1934) showed that the sympathetic system is of paramount importance in the production of the nervous manifestations in amebiasis In addition toxic and allergic phenomena play a role These are due to the disintegration of the amebic tissue to the activity of secondary invaders and to the absorption of allergens through the ulcers In the last five years we have examined bacteriologically and parasitologically stools from more than 700 patients with amebiasis In only 3 per cent of them were we unable to find secondary invaders such as Proteus paracolon organisms flagellates and others It must be considered that these organisms may add to the general so called toxic symptoms so often observed in amebiasis

Craig (1944) stated that amebiasis always causes clinical symptoms even in the so-called "symptomless carrier state" but these complaints may be so mild and the patient so accustomed to them that he either does not pay any attention to them or attributes them to some other cause

Subclinical Amebiasis

This is the symptomless carrier or cyst passer state Most of the patients do not apply for medical care and if they do they generally come to the physician s office or to the clinic for other reasons The majority of such cyst passers are discovered by parasitologic surveys on routine gastrointestinal check ups and when an investigation is carried out by public health authorities to discover the source of infection of a clinically manifest case Upon questioning some cyst passers reveal vague general symptoms such as lassitude fatigue occasional headaches irritability disturbances of sleep and appetite vasomotor manifestations such as a feeling of cold in the extremities palmar perspiration palpitation etc These symptoms as Craig (1944) pointed out are not at all typical of amebiasis If caused by *E his tolytica* however they disappear after antiamebic treatment

The danger of subclinical amebiasis is twofold First clinical symptoms may develop when the host parasite relationship is disturbed There seems to be an equilibrium established between the invading amebae and the defense mechanism of the body of the host If this equilibrium is disturbed in favor of the parasites the process spreads causing amebic dysentery and even liver

abscess Cases of amebiasis of the liver which have developed without clinic intestinal signs and in which practically no bowel lesions are seen origina from symptomless carrier states

Second the carrier is a dangerous source for the spread of amebiasis A stated above the disease is transmitted only by cysts Therefore the cy passer is an effective propagator of amebiasis mainly when he is a foo handler—cook waiter food store clerk marketing vegetable gardener or farme dairy worker etc Under lowered hygienic conditions the stools of a cy passer may contaminate supplies of water used by other people Because o the large number of such cyst passers among the population of the America no effective antiamebic program is possible unless they are cured

Symptomatic Amebiasis—Syndromic Amebiasis

Amebiasis With Prevailing Constipation—Simon (1934) Howard (1939) Manson Bahr (1943) Craig (1944) Lopes Pontes (1945) and others emphasiz *constipation as an outstanding symptom in many cases of amebiasis* In th type of amebiasis designated here as amebiasis with prevailing constipation constipation usually dominates the picture There are however diarrhea episodes mostly in the early morning hours These attacks may be instigated or initiated by certain foods and may be attributed to food allergy or a nerv ous upset may lead to their occurrence Excessive indulgence in alcohol may also bring on an attack The patient is awakened by the necessity for evacu ation of the bowels Pain is usually present either diffuse or localized in the lower abdomen. The pain may even be colicky Colic however is not re ported in very many cases One or more stools terminate the attack These are copious but as a rule do not contain blood or mucus The number of bowel movements does not exceed three to four per day The diarrhea lasts only one or two days Following it constipation commences which is again interrupted by a new attack of diarrhea after a period of two or more weeks to months

Constipation with a consecutive diarrheal attack is also observed It is *characterized by mild epigastric pain or feeling of pressure mainly after* meals and moderate hyperchlorhydria thus resembling gastric or gall bladder disease This form often observed in the Midwestern United States was re cently described in Brazil by Lopes Pontes (1945a)

Distention particularly after eating is a common complaint in amebiasis It is caused by the accumulation of gas and is the source of much discomfort Distressing flatulence and borborygmus are present usually involving the right side of *the abdomen Manson s sign the amebic splash* that is sensa tion of fluidity upon palpation is often observed Discomfort distress or pain may appear in paroxysms lasting one or more hours The pain may re main localized or it may migrate

Gastric disturbance resulting from the distention and consequent reflex pain is frequent The appetite may be capricious *Dislike of certain foods* is not unusual

There is no fever. On the contrary, the temperature trend is toward the subnormal, falling in the morning to 96° or 97° F. (35.5° to 36° C.) as pointed out by Craig (1944).

The general symptoms connected with this type are those described under the heading Subclinical Amebiasis. Lack of concentration and memory, sleeplessness or sleepiness, especially in the morning, and headache in the early hours are very frequent in this type of amebiasis.

These clinical symptoms explain why this disease is often mistaken for nervous irritable or spastic colon, food allergy, neurasthenia, duodenal ulcer, chronic gastritis, and other conditions.

The stools do not show blood, except in very rare instances. A few leucocytes and pyknotic nuclei may be present. Much undigested food is present during the diarrhea. Often several specimens, including postcathartic stools, must be examined before the amebae are discovered. Manson-Bahr (1943) recommended that the feces adhering to the rectal mucosa be examined for cysts. The authors have found this a very helpful procedure.

Amebic Diarrhea. This type differs from the former in the development of a more expressed diarrheal pattern. The disease begins suddenly or slowly. The first attack of diarrhea or the recurrent attack may be caused by many factors, such as excess food, alcohol, nervous upset, etc. The attack is similar to that described under Amebiasis With Prevailing Constipation, except that the stools may be more numerous, as many as ten a day, the average being three to five. In addition, the attack lasts for several days, the stools remaining semifluid for some time. It is not uncommon for constipation of a short duration to follow, mainly in cases treated with intestinal absorbents and astringents.

Colic is usually present. The attacks are terminated by the evacuation of copious light colored or very dark, frequently semifluid stools, with mucus and a few leucocytes. There is definite relief after the evacuation of the stool. Usually much gas accompanies the feces.

The colic or the pain may be diffuse or localized. If localized, the favored sites are in the following order: over the cecum, sigmoid, descending colon, transverse colon, and lumbar region. The sigmoid is sensitive upon deep pressure. This is Manson's "amebic signpost."

The pain often shows definite changes. It may increase with cramps of short duration, changing into a feeling of deep pressure and distention. There is much gas, flatulence, and borborygmus. Flatulence may be the most outstanding complaint of the patient.

The pain may depend upon meals. In many cases there is a feeling of fullness and distention after meals and pain appears within a few hours thereafter. There is no tenesmus.

A mild elevation of the temperature, without great changes in the blood picture, may be observed on the first day of the diarrheal attack. It usually reaches 100° F. (38° C.).

Gastric disturbance and changes in the appetite are present in many cases. While the types of amebiasis described above do not cause loss of weight, this

is observed in amebic diarrhea mainly during the hot season This loss is often compensated during the winter months The nervous symptoms are the same as in the preceding types of amebiasis

The stools contain mucus some leucocytes and pyknotic bodies Many tissue cells yeasts and mold spores are common If the disease is of longer duration Charcot Leyden crystals are not rare

The clinical symptoms of amebic diarrhea must be differentiated from *chronic mucous colitis* *In amebiasis* strings or casts of the bowel are never evacuated Finding amebae will establish the diagnosis Ulcerative colitis and *carcinoma* the *latter resembling solitary amebic ulcers must be differentiated* also by the aid of x ray and proctoscopic examination Intestinal tuberculosis may cause many symptoms *simulating amebiasis* *Constant elevation* of temperature loss of weight lung findings and stool examination will determine the diagnosis It must be pointed out that in the authors' experience the intestines of persons with carcinoma or diseases involving the blood forming organs such as leucemia Hodgkin's disease etc are often invaded by *E histolytica* Therefore if amebae are found they should not be considered as the exclusive factor for other diseases may be present One must keep in mind too that there are no diseases there are only sick people

Intermediate Type of Amebiasis—Many cases of amebiasis cannot be classified The dividing line between the two preceding types is the duration of the diarrhea and the composition of the stools One finds a number of cases which at times show the characteristics of one and at times features of the other type Such cases should be classified as intermediates The most common *of these is the seasonal type* *After excessive eating or consumption of* alcohol often at the time of national or religious celebrations the diarrheal *course develops* with mucus in the stools Then the pattern of constipation is followed through the intervening months reverting to the diarrheal type after new excesses

Irregular bowel action without frank diarrhea with enterospastic symptoms and weakness after defecation as described by Browne et al (1945) is another frequent manifestation of amebiasis which must be classified as an intermediate type

Acute and Chronic Amebic Dysentery—This is the classical amebiasis mostly observed in hot climates and often becoming manifest in persons recently arriving from the tropics

The onset is sudden or gradual If gradual the disease begins with a mild *diarrhea later evacuation of feces* with mucus and blood develops Colic and tenesmus are usually absent during the acute stage Tenesmus may *develop later* as a result of anal irritation The pains may vary in intensity

In cases with sudden onset the pain is generally intense and localized in the same regions as in amebic diarrhea The stools are copious and always contain fecal material In very acute cases as many as twenty five to thirty bowel movements a day are observed The majority however have about five to fifteen stools per day They contain blood streaked mucus *When the* blood is greatly altered and intermingled with mucus and feces " anchovy

sauce" stools are observed. Pinhead sized particles of bloody mucus simulate "sago grains." *Decomposed blood may give the feces a very dark discoloration.*

There is much abdominal discomfort, feeling of distention and pressure. Flatulence is common.

According to Mukherjee (1942) fever is present in about 10 to 15 per cent of the cases. It occurs more frequently in acute forms. It reaches 100° to 101° F (38° to 38.5° C). There is a definite loss of weight during the disease.

In fulminating cases, gangrene of the intestines develops due to secondary infection. In other cases the ulcers penetrate rapidly and cause perforation of the blood vessels with extensive hemorrhages. They may break through the intestinal wall and initiate peritonitis. This form is fortunately rare, and ordinarily a chronic state develops.

Chronic amebic dysentery is characterized by general symptoms as previously described. *Abdominal discomfort and flatulence cause great distress.* There is usually localized pain, mostly above the cecum or sigmoid. The number of stools is increased, or constipation alternates with diarrhea. There may be persistent low grade fever resembling brucellosis or tuberculosis. Intermittent fever with peaks as high as 102° to 104° F (39° to 40° C) has also been reported. During the attack of diarrhea the stools show the characteristics of dysenteric feces: they contain various amounts of mucus and blood.

If the disease is not treated, further developments with several courses may be observed.

In unfavorable cases, loss of weight continues. A "myxinoid" inelastic skin develops. Sequelae and complications arise which kill the emaciated patient.

In more favorable cases the disease may revert to a milder form. Frequently a subclinical state is the outcome. In other instances a type with constipation develops.

As to the differential diagnosis, the classical picture is easily recognized if stool examinations are made. The acute form may resemble typhoid or Salmonella fever. However, the spleen is not enlarged in amebiasis. Differentiation from bacillary dysentery in cases with acute onset and tenesmus may be very difficult. Laboratory examination of fresh stools for both parasitic and bacillary incitants of diarrhea will solve the differential diagnosis.

Amebiasis With Localized Symptoms. *There are forms which are more or less confined to certain segments of the bowel in such a way that the resulting symptoms closely resemble other diseases.* Most important of the manifestations of amebiasis are the following forms:

Amebic Typhlitis and Appendicitis. Because more than 80 per cent of the amebic lesions involve the cecum, symptoms in this region of the bowel are not at all rare. A picture clinically resembling subacute appendicitis is a common feature. When the course is subacute or chronic, pain localized in that region is the *most outstanding symptom.* *Acute amebic ulcers may cause* elevation of temperature to 100° to 102° F ([illegible] to 39° C). Pain is always

present Nausea may be one of the complaints While the pain is localized in the right iliac fossa there is little alteration of the pulse and of the respiration The number of white blood cells may be increased If the number exceeds 15 000 to 16 000 secondary infection must be suspected Such an invasion also causes symptoms of peritoneal irritation to a marked degree so that all clinical signs of such an involvement—signs of Ploenius Rovsing and Blumberg—become strongly positive The differential diagnosis of amebic typhlitis and appendicitis from other diseases of these portions of the bowel is of paramount importance because operation upon the amebic intestines leads to rupturing sutures fistula formation cutaneous amebiasis etc Finding amebae in the stool and prompt reaction of the patient to emetine permit avoidance of grave consequences

Amebic Granuloma—Amebic granuloma is a condition often mistaken for malignancy because the proctoscopic and x ray pictures resemble that of annular carcinoma This condition was recently discussed by Reddy and Rangam (1946) and Silverman and Leslie (1947) Examination of biopsy material will determine the diagnosis as suggested by Smyth (1946)

Amebiasis Resembling Cholecystitis—True amebic cholecystitis is very rare Most strains of amebae are killed by bile But when the lesions are localized in the splenic flexure of the colon or in the transverse colon the symptoms may closely resemble cholecystitis with or without cholelithiasis There is a feeling of pressure dull pain or even cramps in the right upper quadrant often irradiating dorsally and caudally The pressure or the pain becomes worse after meals Intermittent diarrhea may be present For the differential diagnosis the following features are important The typical attack of cholelithiasis causes much stronger pain than does amebiasis Amebiasis only rarely shows icterus On palpation the point of pain is more localized in cholecystitis than in amebiasis Laboratory examination is of the utmost value

Amebiasis Resembling Ulcers of the Stomach or of the Duodenum—Pain beginning two or three hours after meals is often present in mild forms of amebiasis When the pathology is localized in the transverse colon there may be sensitivity to pressure under the xiphoid process of the sternum or to the left side of it In other cases there is heartburn with hyperacidity pain between or shortly after meals feeling of fullness with constipation and dark stools

Other types are relatively rare

Complications

The manifold complications of amebiasis may be divided into intestinal and extraintestinal types

Perforation—These are not very frequent In North America they occur only in about one out of one thousand cases of amebiasis They may develop suddenly or slowly according to the thickening of the wall and peritoneal reactive processes in the vicinity The perforations are usually in the cecum

appendix or rectum *They may be single or multiple* The result depends upon the site of the perforation Most frequent are perforations into the peritoneal cavity causing peritonitis *Perforations into the pericardium and* urinary tract are rare Slowly developing perforations may cause pericolic perirectal, or perinephritic abscess

A sudden perforation is revealed by pain, or colic distention of the abdomen vomiting collapse There is an increase in the pulse rate and in the respiration The temperature may remain subnormal during the first hours Manson Bahr (1943) pointed out that in toxic patients the symptoms are not always so dramatic and the spreading of tenderness may be the only sign of perforation We saw several cases in which the onset of the perforation could *not be diagnosed except for the sudden change in the stools which became* glassy like and consisted of a mixture of mucus and blood without other material *normally present in the feces The perforation of amebic typhlitis or appendi*citis cannot be distinguished from perforations caused by other forms of appendicitis Rectal perforation may be seen through sigmoidoscopy

Abscess formation does not necessarily cause many clinical symptoms if the abscess is small Changes in the blood picture are more extensive when secondary infection is present

Hemorrhage—Hemorrhages originate from the erosion of vessels at the bases of intestinal ulcers Small hemorrhages may be observed also in patients with hemorrhoids when these bleed during an attack of amebic diarrhea or dysentery Hemorrhages always must be carefully investigated and treated accordingly

Amebic Hepatitis—Hepatitis occurs in 0 1 to 5 per cent of cases with amebiasis In the northern parts of the United States where the smaller type of *ameba causes most of the infections hepatitis is very rare Excellent reviews* of this complication were published by Warshawski et al (1946) and Klatskin (1946) *Klatskin (1946) distinguishes the following types acute subacute* and chronic hepatitis which must be differentiated from amebic abscess

The onset is usually sudden There are however cases of intestinal amebiasis with unexplainable short chills which later develop into the classical picture of amebic hepatitis Manson Bahr (1943) believes that chills result from periodic invasions of the liver by amebae There is irregular fever especially in the acute form frequently reaching 102° to 104° F (38° to 39° C) often accompanied by sweating mainly at night The liver is enlarged and painful The pain frequently irradiates mostly to the shoulders less often to the back or upward it increases upon movement pressure inspiration and cough and sometimes by lying on the side While toxic icterus may be present it is an exception rather than the rule The number of white blood cells is frequently between 15 000 and 0 000 The number of mononuclear cells is decreased The sedimentation rate of the red blood cells is increased

Diarrhea is observed in many cases but may be absent Nausea and vomiting are frequent *Cough may be an outstanding symptom*

The attack may subside after a few days or may precede the development of a liver abscess Relapses may occur *or a chronic form may develop*

The subacute and chronic forms show less pain little or no fever and in some cases little or no change in the blood picture

The acute form must be differentiated from amebic liver abscess and other conditions In acute cholecystitis and cholangitis bile pigments are found in the urine A positive van den Bergh reaction and a high icteric index are discovered upon examination of the blood serum Icterus is also present as a rule

The subacute chronic and recurrent types must be distinguished from malaria brucellosis chronic cholecystitis liver cirrhosis stasis in heart disease schistosomiasis and other conditions

Amebic Liver Abscess (Figs 17 and 18)—Craig (1944) reported liver abscess in 5 per cent and Manson Bahr (1943) in 2 to 5 per cent of the cases of amebiasis It is usually a late complication of amebiasis and may also develop in cases where amebae are not found in the intestinal contents

Newcomers to the tropics are more subject to liver abscess than persons born in such a climate Excessive use of alcohol malnutrition and debilitating diseases likewise are predisposing factors for this complication

The acute form with symptoms closely resembling amebic hepatitis is less frequent Usually multiple abscess formation causes the acute symptoms The pain is often relieved by lying on the right side The number of white blood cells is lower according to Klatskin (1946) higher than in amebic hepatitis *There is often nausea or vomiting Diarrhea is frequently absent Coughing* is a usual complaint

The more frequent chronic form begins with a feeling of pressure Later pain develops which often irradiates as the pain in amebic hepatitis It may be more intensive at night The fever is low at the onset reaching its peak *in the evening* Later chills may develop Night sweats may accompany the drop in temperature which becomes normal or even subnormal in the morning Gastric and intestinal disturbances may be absent *The sedimentation rate of* the red blood cells is often increased Cough may cause much complaint The abscess frequently localizes in the right lobe There is pain on palpation and pressure loss of weight and indigestion Pressure of the abscess on the bile channels may, in rare instances cause icterus Any part of the liver may *show enlargement* The right diaphragm is frequently elevated and its movements limited In other cases the lower liver border is shifted caudally Enlargement of the left lobe may cause pressure or simulate enlarged spleen Irritation of the diaphragm and the pleura causes coughing as well as exudation and even compression of the right lower lobe

The abscess may perforate into the abdominal cavity or more often into the lung *If perforation* does not terminate the disease emaciation is the usual cause of death *Only 15 to 30 per cent* of unoperated patients survive

The number of white blood cells is between 10 000 and 35 000 Da Silva (1945) states that the larger the abscess the lower the cell count

When the liver abscess is secondarily infected the fever and the leucocytosis are high Differential diagnosis may be very difficult in such cases

Problems of differential diagnosis are numerous In acute amebic hepatitis there is more pain on palpation The liver is always enlarged in toto while in amebic abscess as a rule only parts show an increased volume Suppurative cholecystitis likewise must be differentiated Pleurisy, chronic pneumonia empyema and tuberculosis may be distinguished by x ray examination Carcinoma of the liver may cause great diagnostic difficulties Subphrenic abscess from perforated ulcers shows gas under the diaphragm Infected hydatid cysts and undulant fever may be excluded by laboratory tests Kala azar malaria and typhoid fever produce leucopenia and spleen enlargement

Other Localizations of the Amebic Abscess — Amebic abscess of the lung is usually due to a liver abscess It contains chocolate colored pus which is expectorated early in the disease Later the pus becomes more of a yellow color and contains Charcot Leyden crystals The x ray examination shows a picture similar to bronchopneumonic consolidation Fever may or may not be present The white blood cell count is high There is pain cough and hiccup The condition is nearly always fatal

The same is true of brain abscesses which cause symptoms according to their localization Abscess of the spleen epididymis and penis and paranephritic abscess have also been described

Cutaneous Amebiasis —This condition recently analyzed by Wilson and Hurewitz (1946) seldom develops The usual site is around the anus or after operation establishing an artificial anus in an amebic intestine or open drainage Punched-out ulcers or irregular spreading ulcerations with granulating painful bases are observed

Urinary Amebiasis —It is an accepted fact that such types of amebiasis are very rare They occur as sequelae of perforation of an amebic intestine or abscess into the genitourinary system according to Watson (1945 1945a) Amebiasis of the sexual organs is rare

Sequelae

Progress of amebiasis may lead to permanent changes in the intestine These together with the reactions of the autonomic nervous system discussed and classified recently by Lopes Pontes (1949a) and allergic phenomena create a number of changes causing the patient considerable distress

Spastic Colon —Spastic colon indistinguishable from spastic or "irritable" colon of other origin may result from amebiasis It develops chiefly in persons who have suffered from much constipation during the amebiasis There are spastic contractions of the colon particularly of the descending large bowel These contractions alternate with periods of relaxation even hypoactivity of the colon This sequel is very frequent in North America

Mucous Colitis —Manson Bahr (1945) emphasizes this sequel In our observations of mucous colitis which develops in amebiasis there are not many eosinophiles in the stools Finding of large casts of the bowel in the feces is also rare Varying amounts of mucus are expelled with the stools which may vary from day to day in the same patient

The subacute and chronic forms show less pain, little or no fever, and in some cases little or no change in the blood picture

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Postamebic Gastrointestinal Disturbances—This condition may be characterized by hyperchlorhydria or by hypochlorhydria. It is the result of a combination of the nervous disturbances to which the lessened ability of the diseased intestines to absorb the B vitamin complex (Ascoli 1946) adds further reasons for dysfunction. As in the preceding conditions it may originate *during the* actual amebiasis and become predominant during convalescence. It often presents therapeutic difficulties, especially if for some reason an adequate diet cannot be sustained.

Intestinal Ulceration—Manson Bahr (1945) points out that ulcers of the small intestine may appear as a sequel to amebiasis.

Chronic ulcerative colitis of the large bowel is *often* observed either as a complication or as a sequel to amebiasis. Secondary infection and disturbances of bowel innervation play a major part in its development. The clinical picture does not differ from that of the so called "idiopathic" ulcerative colitis.



Fig 19.—Amebic colon showing typical ulcerations. A defect penetrating the entire wall is due to the great fragility of this diseased tissue. (*From the collection of R. B. H. Gradwohl.*)

Hill Diarrhea and Sprue—While many authors consider these conditions as separate entities *sui generis*, others see amebiasis as the cause. Hill diarrhea like conditions of *different intensity* are often observed immediately following amebiasis. Disturbances of fat absorption are not rare in chronic amebiasis.

Malformations of the Colon—Strictures and stenoses are rarely sequelae of amebiasis. Rather dilatations and diverticula tend to develop. Megacolon has been observed. These conditions *are diagnosed by x ray*.

Diseases of the Rectum—Prolapse of the rectum and hemorrhoids are not infrequent, particularly in long-standing cases. Periproctitis with or without abscess formation may result chiefly in patients with extensive secondary infections.

Malignancy—Manson Bahr (1945) calls attention to carcinomatosis originating in amebic and postamebic lesions Reed and Anderson (1936) described a number of cases with malignancy observed after amebiasis This sequela however seems to be rare

Nephritis—Interstitial nephritis is often observed in fatal cases of amebiasis Nephritis may develop during the acute phases of amebiasis and is frequently overlooked if periodic urine examinations are not carried out The pain in the back may be attributed to the diseased intestines which holds true in most patients who complain of such pain A latent nephritis is frequently discovered through the use of nephrotoxic drugs in the treatment of the amebiasis

Neurasthenia—Neurasthenia acompanies all types of amebiasis Craig (1944) stated that many cases of ' tropical neurasthenia ' are caused by amebiasis

SIGMOIDOSCOPIC EXAMINATION

Manson Bahr (1945) found lesions during sigmoidoscopy in about 50 per cent of his cases Browne et al (1945) in about 18 per cent Karl and Sloan (1946) in about 30 per cent Many cases do not show such changes The lesions are often microscopic and must be observed according to Manson Bahr s recommendations through a magnifying glass

One must emphasize that the sigmoidoscopic findings are often not paralleled by the clinical picture Sometimes extensive lesions and only few clinical symptoms are observed while in other cases scant pathology will be manifested by severe clinical features

The rectosigmoidal junction and Houston s valves are the most frequent sites of visible lesions

Often only small elevations with hyperemic margins are seen There may be small depressions granular patches or scattered hemorrhages An unchanged mucosa between the lesions is typical of amebiasis where secondary infection has not taken place

Typical ulcers with undermined edges easily bleeding bases and hemorrhagic margins covered with exudate and debris may be seen Large solitary ulcers are rarely observed When they do occur their usual location is just inside of the anal margin They are painful and bleed easily When the ulcers spread they may coalesce and form larger easily bleeding defects

X RAY EXAMINATION

Vallarino (1925) called attention to filling defects in amebiasis Weber (1933) and Bell (1938) consider a cone shaped deformed cecum characteristic of amebiasis Ikeda (1934) stated that the x ray picture differs according to the type of amebiasis that is if ulcerative fibrous or granulomatous processes predominate Recently Walbur and Camp (1946) and Arendt and Cohen (1948) revised the roentgenology of amebiasis with the aid of studies of the mucosal pattern Deformities of the cecum were often found A



g 20 — X ray picture of bowel in amebiasis (Courtesy of Dr Arendt and Dr Cohen and the Am J Roentgenol & Radium Therapy, 1946)



21 — X ray picture of bowel in chronic ulcerative colitis (Courtesy of Dr Arendt and Dr Cohen and the Am J Roentgenol & Radium Therapy 1946)

barbed wire appearance of the bowel similar to that seen in irritable colon" was observed In addition swelling and widening of the mucosal folds their disorientation chiefly in the ascending colon and cecum, were present The mucosal folds ascended with sharp angles Soft double outlines showed swollen intestinal walls Localized spasm over the cecum and ascending colon with irregular feathery pattern was frequently seen In other cases a narrowing of the sigmoid was observed A wider system with fewer mucosal folds caused a paucity of the mucosal pattern in many cases. When chronic ulcerative colitis entered the picture mucosal denudation in the descending colon developed In other cases wall defects fibrosis contraction and absence of haustration or a corkscrew type of incomplete haustration were seen

Arendt and Coheen (1948) found a mild degree of mucosal irregularity also in *Dientamoeba fragilis* and *Iodamoeba butschlii* infections



Fig * —X ray picture of bowel in bacillary dysentery (Courtesy of Dr Arendt and Dr Cohen and Am J Roentgenol & Rad'n Therapy 1946)

LABORATORY FINDINGS

Stool Examination

The laboratory proof of amebiasis is the finding of *E histolytica* As a rule in formed stools one finds cysts while in liquid stools trophozoites predominate

The methods of examination are described in detail in Chapter 71 and by Gradwohl (1948)

It is imperative to examine every stool for both parasitic and bacillary irritants of diarrhea

The cellular composition of the fecal material may give a hint as to the diagnosis In the beginning of amebiasis the exudate contains only a few

leucocytes and extruded *nuclei of white blood cells called* 'pyknotic bodies' by Callender These bodies are a constant finding in clinically manifest amebiasis If red blood cells are present in larger numbers they may show clumping During the later development of amebiasis Charcot Leyden crystals may appear Manson Bahr (1945) warns against overestimating their importance They *are not specific for amebiasis Undigested food* mycotic elements and many epithelial cells are frequently found When secondary infection develops the picture may be changed

Amebae usually disappear from the stools during a severe intercurrent bacillary intestinal disease such as *typhoid or Shigella dysentery When* these conditions clear the amebae reappear *Exceptions however, are often* encountered when *E histolytica* is found and simultaneously Salmonellae or Shigellae are cultivated

In order to be able to evaluate the results of therapy, the first stools after treatment must not be taken sooner than five days after discontinuation of the therapy Three examinations should be performed one week apart Then for six months monthly examinations are advised When the lesions are restricted to the upper parts of the large bowel postcathartic stools are preferred

Complement Fixation Tests

In cases where amebae are not found and suspicion of amebiasis persists complement fixation tests may be performed These are carried out with antigens prepared from alcohol extracted amebae according to Craig (1942) More recently the alcoholic antigen of Rees (1942) has become commercially available The method of Bozicevich Hoyem and Walston (1946) (Gradwohl 1948) is recommended

The complement fixation test is most valuable in amebic liver disease It becomes negative after the disappearance of the amebae

Blood Picture

There is no blood picture characteristic of amebiasis A microcytic anemia is frequently seen *The red blood cell count is between* 4 000 000 and 5 000 000 the hemoglobin is 65 to 80 per cent, sometimes higher

In acute stages the white blood cell count is higher than in bacillary dysentery In chronic cases without complications it is below 12 000 The lymphocytes may be increased and a slight monocytosis may exist An increase in the number of the eosinophiles is observed only in some patients

PROGNOSIS

If all types of amebiasis are considered the disease appears as a relatively mild illness with little mortality When clinically manifest cases alone are taken into consideration the mortality will be between 2 and 4 per cent This varies however with the locality and intensity of the disease While amebiasis in North America is generally mild during the severe Chicago out

break in 1933 the mortality reached 7 per cent About 40 per cent of patients with amebic typhlitis and appendicitis die when operated upon

Abscess formation makes the prognosis serious When a liver abscess perforates into the lung the prognosis is still somewhat better than if perito neal perforation occurs Brain abscess intestinal perforations and fulminant gangrenous cases of amebic dysentery are nearly always fatal

TREATMENT

Treatment of intestinal amebiasis consists of four factors antiprotozoan dietary supportive and symptomatic All of these are of great importance and must be carried out systematically During and after the course of ther apy one must bear in mind that only in a fraction of the clinically manifest cases is the treatment finished when the stools are free from amebae Many patients will require some special attention because of secondary infection and sequelae Careful analysis of the clinical sigmoidoscopic and x ray findings as well as stool studies will help to ascertain the best method for eradication of the residual troubles Excellent discussions of the antiamebic drugs have been published recently by Manson Bahr (1943) Craig (1944) Klatskin (1946a) Karl and Sloan (1946) Raul (1947) Arnett (1947) and others

Antiamebic Drugs

Emetine —This is the oldest and most highly valued drug Experience however has shown that emetine does not kill the amebae but simply allevi ates the toxic symptoms On the other hand this drug in itself is very toxic Acting directly upon muscle fibers it causes true myositis The heart muscle suffers most frequently (Dack and Moloshok 1947) The first signs of emetine intoxication are usually a drop in the blood pressure and irregular heart action Tachycardia is often present The patient is weak and may complain of paresthesias Diarrhea is not rare Symptom complexes re sembling neuritis have been described Progressive muscular atrophy and trophic disturbances of the skin of the hair and of the nails have also been observed Children and pregnant women are very sensitive to this drug therefore it should not be prescribed for them Manson Bahr (1943) called attention to the fact that amebae may become emetine resistant if the drug is not used wisely

In order to carry out the treatment in the most proper manner the pa tient must remain in bed during the course of treatment and for three days following it Blood pressure and pulse rate must be watched carefully The treatment must be discontinued immediately if the blood pressure drops, the pulse frequently increases or other signs of emetine intoxication appear

Oral emetine treatment is new in America (Shrapnel et al 1946) Em etine by mouth causes emesis and is less effective Intramuscular injections are preferred by many authors Some writers warn against the subcutaneous route because of the possible sensitivity of the skin The drug must never be given per rectum or into the veins

*See also Chapters 65 and 66

The daily dose is 0 06 Gm best divided into two portions 0 03 Gm in the morning and the same amount in the evening The duration of the treatment is six to seven days never longer than eight to ten days If the emetine helps it causes cessation or partial relief of the symptoms within the first four days There is little use in continuing the drug on or after the fifth day if the condition of the patient has not improved

A second course of emetine should not be given until at least three months have elapsed since the first course of treatment with emetine Longer courses are advocated by Klatskin (1946 and 1946a)

Emetine is the only known drug which acts upon amebic tissue (Parmer 1948) In spite of its toxic action it must be used Indications for emetine treatment are

1 Amebic dysentery
2 Acute or subacute amebic typhlitis and appendicitis
3 Amebic hepatitis
4 Amebic abscess

Contraindications of emetine therapy are

1 Children
2 Pregnant women
3 Emaciated cachectic patients
4 Cardiac disturbances including sclerosis
5 Forms of amebiasis not listed as indications for emetine therapy

Emetine bismuth iodide contains 25 to 30 per cent emetine It is given by mouth in gelatin or salol coated pills It is best used according to the principle of Manson Bahr (1943) which with some changes is given below

The patient is put to bed for the duration of the treatment and for three additional days Fasting for three to four hours before the pill is taken is essential The drug is given late in the evening The treatment lasts for ten to twelve days during which period the patient receives a total of 1 65 to 2 Gm of the drug 0 05 Gm the first two days 0 1 Gm the next two days and then 0 2 Gm per day are given together with a light sedative

The indications and contraindications for this treatment are in our opinion the same as for emetine injections The patient is observed as when emetine is injected Vomiting is a very unpleasant *effect of emetine-bismuth* iodide often forcing discontinuation of this medication

Derivatives of Arsonic Acid —*Carbarsone* Amebarson p carbamino phenylarsonic acid with about 28 per cent As is given in gelatin *capsules* containing 0 25 Gm of the drug two capsules a day for ten days It is also available in tablets

Carbarsone in powder form may be used for enemas After a cleansing enema 200 c c of a warm 2 per cent solution of sodium bicarbonate and 1 per cent carbarsone are introduced The patient must retain this enema for at least three to four hours This is easily accomplished when the patient lies in bed and is allowed to change his position every hour A mild sedative may be given

Children receive 0 025 Gm carbarsone per year of physical age every day The treatment lasts for ten days

Acetarsone Stovarsol Kubarsol Spirocid Fourneau 270 3 acetylamino-hydroxy phenylarsonic acid containing about 27 per cent As, is used in the same dosage as carbarsone It is, however absorbed from the intestine

Both drugs are toxic for the liver and kidneys They may cause symptoms of arsenic intoxication such as colic diarrhea and dermatitis

According to Craig (1944) arsenic preparations should be reserved for cases in which iodine preparations (and if indicated also emetine) have proved unsuccessful The author suggests the use of carbarsone mainly in children who cannot receive emetine and in combination with other drugs

Neoarsphenamine was tried by Bruce (1946) *Vilibis* has little effect

Iodine Preparations—*Chiniofon* Quinoxyl Kubalen, Anayodin, is a mixture of 4 parts of 7 iodo 8 hydroxyquinoline 5 sulfonic acid or its sodium salt containing 28 to 29 per cent iodine and 1 part sodium carbonate

Chiniofon is an excellent antiamebic drug Sometimes it causes diarrhea which is often stopped by bed rest and strict diet Manson Bahr (1943) recommends that this drug be given with small amounts of opium for example 0 03 Gm t i d Craig (1944) had excellent results with chiniofon

Chiniofon is available in pills or tablets containing 0 25 Gm There seems to be disagreement concerning the dosage of this drug A course of 3 to tablets a day after meals for seven to ten days is recommended After one week interval the treatment may be repeated Others prescribe one pill t i d the first day two pills t i d the second to the fifth day and three pills t i d on the sixth and seventh days Then for three weeks two pills t i d are given every Friday Saturday and Sunday

Children receive one tablet for each five years of physical age every day for a period of ten days

For rectal application 200 c c of a 2 to 3 per cent solution are given after a cleansing enema It is recommended that the patient follow the same precautions as in rectal therapy with carbarsone The enemas are repeated every day for five to ten days

Vioform Enterovioform Protozida is iodo chloro hydroxyquinoline with 37 5 to 41 5 per cent iodine It is a much used drug It may cause irritation of the gastrointestinal tract mainly of the stomach It cannot be given per rectum

Vioform is available in pills tablets or gelatin capsules with 0 25 Gm of the drug Adults receive one to two tablets t i d after meals for ten days After an interval of one week the course may be repeated Children take one tablet per day for each five years of physical age for the period of ten days

Diodoquin diiodohydroxyquinoline contains 63 9 per cent iodine It causes very few secondary effects This was emphasized by D Antoni (1942)

In the author's experience only one case of iodism and two cases of irritation of the bowel occurred among more than 430 patients On the other hand, approximately 76 *per cent* were cured

Adults receive 2 to 3 tablets t i d *after meals for twenty days.* After a one week interval the treatment may be repeated Children receive 2 tablets a day for each five years of physical age for ten days

Diodoquin is the oral drug of choice but is not given per rectum

Combined Treatment—Manson Bahr (1943) gives emetine bismuth iodide by *mouth* and chiniofon in enemas for ten days This treatment requires sedation to be given *during the course* Of 535 cases of amebic diarrhea and dysentery only 1 4 per cent showed relapses after this treatment

Craig (1944) suggested that amebiasis be treated according to the type of the disease He recommends emetine and chiniofon in amebic dysentery and chiniofon or Diodoquin in other types If these drugs do not act in a satisfactory way Carbarsone is given The dosage of the drugs is regulated by the *severity of the disease*

For a combined Protozida and Kubarsol treatment Amebo Oral "Kuba" is used Adults receive 4 to 8 tablets a day and children 1 tablet for each five years of physical age a day

Browne et al (1945) concluded that differences in various schedules of treatment are unimportant

We feel that each drug has its own field of indications and contraindications The choice of an iodine preparation may be difficult One should keep in mind that if one of them is not tolerated or does not act another may be used with success We use Diodoquin in moderate cases and for children Chiniofon is indicated in severe conditions since it may be given *rectally* Carbarsone is used more than Acetarsone *Table IV shows our schedule of treatment*

Other Drugs—*Bismuth subnitrate* was widely used before more effective drugs were devised Now it is restricted to the treatment of postamebic diarrhea

Kaolin bolus alba in large doses as much as 50 to 100 Gm a day as an intestinal absorbent is often given *It may however also absorb the antiamebic drug which is administered Therefore it is preferably used between* periods of active antiprotozoan treatment

Antimalarial drugs as Aralen and Pentaquine, have recently been used alone or in combinations

Kurchi bark from *Holarrhena antidysenterica,* used as kurchine hydrochloride 0 03 Gm to 0 06 Gm subcutaneously or as kurchine bismuthiodide 0 3 Gm by mouth has a questionable curative effect

Chaparro amargoso is derived from *Castela nicholsoni* an American plant Its bark and leaves are used in decoctions and infusions The dosage is 3 teaspoonfuls a day for ten days or enema of 250 to 500 c c *Comprehensive* statistics on the action *of this drug* are *still* lacking

Sulfonamides are beneficial in heavy secondary infections Especially sulfadiazine is recommended by Karl and Sloan (1946)

TABLE IV TREATMENT OF AMEBIASIS

TYPE OF AMEBIASIS	FIRST TREATMENT	CONTRAINDICATIONS	INTERMISSION	IF UNSUCCESSFUL, TREATED WITH	CONTRAINDICATION	SECOND TREATMENT IF NECESSARY
Subclinical and patients with constipational type	Diodoquin, 2 3 tablets t i d for 20 days	None	10 days	Carbarsone, 1 tablet b i d for 10 days	Liver and kidney disease	Repeat Diodoquin or chiniofon, 2 3 tablets t i d for 10 days
Amebic diarrhea intermediate forms syndromic amebiasis without toxicity	Diodoquin, 2 3 tablets t i d for 20 days	None	1 2 days	Carbarsone 1 tablet b i d for 10 days, and chiniofon enemas, 2 5 Gm for 5 to 10 days	Liver and kidney disease	Repeat Diodoquin, or if unsuccessful in first course, chiniofon 2 3 tablets t i d for 10 days
Toxic amebiasis, amebic dysentery	Either emetine injection, 0 03 Gm b i d for 5 7 days, or emetine per os always with chiniofon per rectum for 5 10 days	Heart disease	1 2 days	Carbarsone, 1 tablet b i d or enemas for 10 days if not tolerated Diodoquin 2 3 tablets t i d for 10 days to 20 days	Liver and kidney disease	Vioform, 1 2 tablets t i d for 10 days, repeat after 7 days intermission
		Severe liver or kidney damage			None	
Amebic hepatitis and other extraintestinal forms	Emetine injection, 0 02 Gm b i d for 5 10 days	Heart disease	1 2 days	Revise diagnosis Aralen 0 25 Gm t i d for 10 14 days	None	Treat amebic intestine (penicillin, sulfonamides)
Amebic abscess	Emetine injection, 0 03 Gm b i d for 5 10 days and puncture	Heart disease	According to case	Surgery	Severe cachexia	Penicillin, sulfonamides
Fulminating amebiasis	Emetine injection 0 03 Gm b i d for 5 to 10 days	Heart disease	0	Chiniofon enemas for 10 days		Penicillin, sulfonamides
	Penicillin G 300,000 U	None				
	Bacitracin 120 000 U daily	None				

Emetine, penicillin, and *sulfonamides* are combined by Blanc and Siguir (*1946*) and Klatskin (1946), especially for acute cases and liver complications

While this book has been in press, the following antibiotics have been found effective in amebiasis aureomycin 2 Gm *per day for ten days*, bacitracin 60,000 to 150,000 U per day for ten days Neomycin 100,000 U daily per os, eventually combined with bacitracin Chloromycetin 2 Gm per day for ten to fourteen days

Dietary Treatment

While diet must not be restricted unduly and enough should be given to support life adequately, it is dangerous to neglect the diet D'Antoni (1942) first described a practical diet to be followed in dysentery that takes into account the food habits of the Americas and that can be easily carried out This diet was originally devised for the treatment of bacillary dysentery We have recommended it in more than 800 cases of both chronic protozoan and bacillary dysentery With a few adjustments for the requirements of the amebic patients, we recomend the diet as follows

Permitted All types of bread, preferably toasted, crackers, breakfast cereals, lean and well done beef, lamb, fowl, rabbit, game, veal liver and tongue, puréed cooked vegetables such as beets, eggplant, spinach, tomatoes, green peas, lettuce, cauliflower, Irish potatoes, rice, sago, cooked prunes, apples, baked apples, pure cream and noodle soups, salt, *macaroni, spaghetti, vermicelli* noodles

Restricted 1 or 2 cookies or biscuits a day, once a week, milk pudding, bacon, brain, lean pork, once or twice a week, boiled, baked, or fried trout, pike, red fish or haddock, juices of tomatoes and vegetables, once or twice a week, *prune or pineapple juice raw tomatoes and alligator pear, puréed* carrots, artichokes, string beans, asparagus, raw or stewed pears, apples, bananas, peaches, cottage cheese, American and Swiss cheese, scrambled or poached eggs, 4 a week, one glass of milk a day, or less, one cup of coffee or one to two cups of cocoa a day, tea, vegetable fats, smoking

Not permitted cakes doughnuts, pies syrup chocolate, *Jello, candies*, veal, with the exception of liver and tongue, fat meats hamburgers, sausages, salami, kidneys, corned, dried, or cured meats, sardines anchovies, and fish not listed as "permitted", vegetables and fruits not listed as "permitted", greasy soups, sauces, pepper, paprika, vinegar, carbonated and alcoholic beverages, *root beer, ginger ale, chili* sauce ketchup honey, nuts, pickles, spices

This diet is empirical Carbohydrates and vegetables with strong fibers are restricted in it, as well as irritating food Milk and milk products, which are frequently the source of abdominal discomfort in gastrointestinal disturbances and *often* cause allergic phenomena, are practically eliminated The diet is easily tolerated The restriction of sweets, ice cream, candy, and carbonated beverages is often resented by young people, particularly in summer We found that it is better to add to the *diet orange, pineapple and* grape juice, strongly diluted with water, than to forbid all beverages and have

the young patient consume sodas and sundaes topped with carbonated drinks Weak tea hot or iced with flavor if desired and Postum may be used to quench thirst and aid in the maintenance of a high fluid intake an important point in dealing with progressive diarrhea

Patients in acute stages are put on a high caloric low residual diet At least twice a day some chopped well done beef and beef broth or chicken soup must be given with boiled potatoes or well cooked rice Once a day puréed tomatoes beets eggplant spinach or okra are served Small pieces of white toast with butter supplement the meals Weak tea and weak cocoa without milk tomato and prune juice diluted orange and pineapple juice are given During this acute stage the food must be given every two to three hours in small portions

It is essential that a patient with acute dysentery remain in bed

Supportive Treatment

Every case of clinically manifest amebiasis needs supportive treatment with liver and vitamins Because of the impaired intestinal absorption of vitamins only parenteral administration is really effective Intramuscular injections are preferred In the beginning three and later two injections per week are recommended Each injection consists of 3 to 5 c c of crude liver extract and at least 5 mg thiamine hydrochloride and 75 mg ascorbic acid According to the condition of the patient the injections are continued for two to three months and then the series is repeated eventually with only one injection *a week* Folic acid 5 to 20 mg per day is very beneficial

Symptomatic Treatment

Postamebic diarrhea and flatulence usually subside under the following treatment

Kaolin	0 3 Gm
Magn oxide	0 2 Gm
M f p D t d No 20	
S 1 powder t i d p c	

Commercial combinations of kaolin and magnesium or of kaolin and pectin are also useful

Spasm and pain in the abdomen promptly react to

Papaverini hydrochlor	0 4 Gm
Novatropini sulphur	0 00 3 G
Acid. phenylethylbarbit	0 2 Gm
Sacchari	5 0 Gm
Div in dos No 20	
S 1 powder t i d	

Synthetic drugs acting like papaverine (Pavatrine) are also useful

Constipation may be treated with paraffin oil sodium or magnesium sulfate One to three teaspoonfuls of the sulfates are given in some water before breakfast Sodium phosphate is also effective

If the diarrhea does not disappear and the stools do not contain pathogenic organisms Manson Bahr's prescription (1943) is very helpful

Tannic acid	10 0 Gm
Quinine hydrochlor	1 0 Gm
Warm water	2 L
M D S Enema	

When secondary infection with proteolytic organisms is present sodium sulfaphthalidin 3 to 6 Gm a day for five to ten days may be used Sulfadiazine is given as in bacillary dysentery

Enemas with 1 500 to 1 1 000 Rivanol are also effective

Treatment of Complications and Sequelae

Amebic Liver Disease—Strict bed rest is indicated and emetine is injected Hot packings applied without pressure alleviate the pain

If an abscess of the liver is diagnosed aspiration is performed This is carried out in an operating room so that more extensive surgery can be performed immediately if need arises during the puncture Either a special puncture needle or that routinely employed for lumbar puncture is used Some workers prefer full sized aspiration needles It is advantageous to use an aspirator

Local anesthesia is given In sensitive patients general narcosis must be applied The puncture is performed in the direction of the most prominent portion of the liver upward inward Only abscesses of the right lobe are accessible for aspiration The needle must not be introduced deeper than 10 cm to avoid large vessels The pus is chocolate brown or red and thick with pieces of necrotic tissue Yellow or green pus signifies secondary infection The pus aspirated at the first puncture does not contain amebae When the pus becomes thinner in the course of repeated aspirations amebae may appear

After aspiration 100 000 units of penicillin are injected into the cavity The patient receives 200 000 units of penicillin and some soluble sulfonamide drug for example sulfadiazine on the days when aspirations are performed The injection of 10 c c of Lipiodol and 100 000 units of penicillin into the abscess cavity is very beneficial Penicillin G is preferred

Surgical operation is indicated when (1) inaccessible or multiple abscesses are present (2) hemorrhages occur, (3) there is a secondary infection which resists treatment with antibiotics and sulfonamide drugs (4) the abscess does not show a tendency toward healing, (5) fever persists (6) perforation of the abscess occurs

Before operation penicillin and sulfonamide drugs are given When gram negative rods are present in the pus, streptomycin must be used Usually either the transperitoneal or the transpleural route is used followed by drainage Adequate use of antibiotics and sulfonamide drugs reduce the operation hazards

Intestinal Perforation—While operation on a nonperforated amebic intestine is contraindicated, it is imperative to attempt surgical correction of a perforated bowel. Extensive resection is the method of choice. In dealing with a perforated amebic appendicitis, make drainage through a small surgical incision. The prognosis is always very serious.

Bleeding—Manson-Bahr (1943) recommends cecostomy, when the usual styptics and lavages do not control the bleeding. After the operation lavages with styptics are carried out through the artificial anus. Transfusions of whole blood and plasma, 300 to 500 c c for adults are beneficial.

Malformations of the Colon—Excision of the diseased parts is recommended if strictures or stenosis have developed. If there is no danger to life, one should wait with such an operation until the amebae disappear from the stool.

PROPHYLAXIS

Craig (1944) recommended 1 to 3 tablets of chiniofon a day while sojourning in a heavily infested locality.

General hygienic measurements are essential: (1) survey of the population, principally of food handlers and food workers, (2) treatment of all infected persons, (3) adequate food and water control. If these measures are impractical: (1) drink only boiled water and (2) eat only adequately boiled food served by clean food handlers.

AMEBIASIS CAUSED BY OTHER AMEBAE

The amebae usually found in the human intestines are *Endamoeba histolytica*, *Endamoeba coli*, *Endolimax nana*, *Iodamoeba butschlii*,* and *Dientamoeba fragilis*. There is no doubt concerning the pathogenic power of *E histolytica*. Many authors, however, believe that only this ameba is able to cause amebiasis. A few observers have described pathologic conditions in which other amebae have played an important role. In the most recent literature, Derrick (1945) and Kaufman (1945) reported amebiasis due to *I butschlii*. Some advocate that *D fragilis* is definitely pathogenic, for example, Halawani (1933), as is proved also by the x ray findings of Arendt and Cohen (1948).

PATHOLOGY

Amebae other than *E histolytica* do not produce lesions similar to those found in amebic dysentery, as seen at autopsy. Tissue invasion, however, has been noted at autopsy.

CLINICAL SYMPTOMS

In patients diagnosed by us as having iodamebiasis or dientamebiasis, vague pains in the abdomen and "mushy" stool, rarely true diarrhea lasting a few days were present. Most of the patients were children. In adults constipation interrupted by diarrhea was the rule. Abdominal distention and borborygmus were common. One case of dientamebiasis resembled chronic appendicitis. The stools very often contained mucus. Blood was never found.

LABORATORY FINDINGS

The stools contained undigested food, only a few epithelial cells and, rarely, a few leucocytes. The amebae were numerous. Because of the quick disintegration of both species of amebae in the stools, the examination must be carried out with even greater haste than for *E histolytica*. We found hematoxylin stained slides indispensable for the diagnosis of these

**Iodamoeba williamsi.*

amebiae The use of a higher per cent strength of acetic acid, 10 to 20, is often recommended to afford better preservation of the structures of *I butschlii* and *D fragilis* The procedure described in Chapter 71, however, gives satisfactory results in most cases

No significant changes in the blood picture were observed A microcytic anemia existed in the chronic cases

TREATMENT

Diodoquin, 2 to 3 tablets t i d for twenty days, rendered excellent service Children were given 1 tablet a day for each five years of physical age for the same period The diet was adjusted as for amebiasis caused by *E histolytica*

GIARDIASIS

Giardiasis is a disease of world wide distribution, caused by *Giardia lamblia*, a flagellated protozoan

PATHOLOGY

No satisfactory autopsy reports are available The x ray findings of Welch (1944) show functional rather than anatomic changes It is theorized that Giardiae irritate the mucosa and cause disturbances in the motor activity The organism is most frequently found in the duodenum and often invades the gall bladder

CLINICAL SYMPTOMS

Brown (1945) called attention to the fact that children show more symptoms than adults The complaints consist of abdominal distention, feeling of pressure, and dull pain usually under the right ribs, increasing between meals The pain often is not localized so precisely It may migrate into the area under the xiphoid process of the sternum or other areas Even short colics may be observed Manson Bahr (1943) distinguished acute and chronic recurrent giardiasis In the latter type, constipation may alternate with diarrhea

The number of stools in the diarrheal period is two to ten, usually three to five a day They are liquid, later semisolid or solid containing mucous but no blood They may be sprue like The odor is often very offensive

While about 3 to 18 per cent of the population of the Americas harbor Giardia, according to the geographic position, only a few of the infected persons show clinical symptoms, therefore, a subclinical type of giardiasis must be accepted.

The clinical picture often resembles that of duodenal ulcer or chronic enterocolitis The differentiation is easy with the aid of the laboratory

LABORATORY FINDINGS

Motile trophozoites are more frequent in liquid stools and in gall bladder contents Formed stools usually contain cysts, which are found with relative ease Children often show microcytic anemia

TREATMENT

Brumpt (1937) introduced Atabrine in the treatment of giardiasis This drug is best given 0 1 Gm t i d for seven days Children over 10 years receive 0 1 Gm b i d for five days Because of its toxicity in small children, Atabrine must be replaced by carbarsone or iodine preparations, in the same doses as in the treatment of amebiasis

COCCIDIOSIS

This is a very rare infection in human beings, caused by *Isospora hominis*, a parasitic sporozoan Kiskaddon and Renshaw (1945) collected 213 cases from the literature Consentino (1945) described one in Brazil, Beltrán (1943) in Mexico, and Humphrey (1946) in the United States

PATHOLOGY

The organism does not invade human tissue No autopsy reports are available

CLINICAL SYMPTOMS

In the two cases which we observed, only mild diarrhea was present without pus or blood but with much mucus in the stools The feces were light colored and liquid and had an offensive odor There were no general complaints Both patients recovered within five days

LABORATORY EXAMINATION

Characteristic spores are found in the stools which contain undigested food some epithelial cells and mucus Many authors have described Charcot Leyden crystals in the feces

TREATMENT

The disease is self limited No therapy is necessary

BALANTIDIASIS

Balantidiasis designates invasion of the intestines by *Balantidium coli* a ciliated protozoan

AGENT

The disease is transferred from pig to man or from man to man by contaminated food or water Also farmers handling infected animals and butchers or abattoir employees become infected The infective form is the cyst which is very resistant to outside agents The cysts are able to survive in feces and in water for weeks but are easily destroyed by sunshine

PATHOLOGY

The findings are similar to those in amebiasis The organisms penetrate between the cells of the columnar epithelium and the Lieberkuhn cysts and descend to the basement membrane of the mucosa If bacteria do not accompany the balantidia no inflammatory reaction is observed in this stage Later cytolysis with consequent suppuration develops The balantidia are found also in tissue without reaction or with little reaction They may show degenerative changes which begin with karyorrhexis The areas of suppuration are later surrounded by fibrosis

After the necrotic tissue debris becomes detached from the intestines irregular ulcers with undermined edges are seen The mucosa between the ulcers is intact except for occasional small hemorrhages Secondary infection may alter the picture If the ulcers heal fibrotic scars are formed

CLINICAL SYMPTOMS

Recently Jaffe and Kann (1943) described balantidiasis as occurring frequently in Venezuela Beltran (1942) found fifty nine cases in Mexico Tsuchiya and Kenamore (1945) reported on balantidiasis in the United States

The clinical symptoms are the same as in amebiasis Invasion of the intestines by balantidia may be symptomless as in the case observed by us If clinical signs of disease are present, they vary from uncertain, vague ab-



Fig 23 —Base of balantidial ulcer (Original photomicrograph of Oscar Felsenfeld)

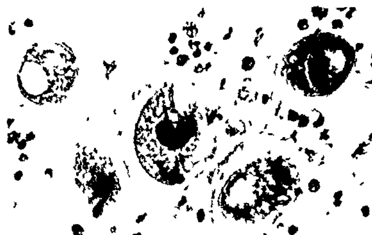


Fig 24 —Degenerating balantidia in the *intestine* (Original photomicrograph of Oscar Felsenfeld)

dominal discomfort to acute dysentery Pain and tenderness may be localized over the cecum There is *either constipation alternating* with diarrhea, or a chronic diarrhea, with three to fifteen stools a day, which are semifluid or

fluid and light colored or greenish and have an offensive odor While mucus is regularly found, blood appears only in acute cases The disease cannot be differentiated from amebiasis without stool examination

LABORATORY FINDINGS

The stool contains many balantidia in the beginning, but few leucocytes Later the number of balantidia decreases and the number of leucocytes increases Mucus is almost always present Charcot Leyden crystals may be present In uncomplicated cases the blood picture is essentially normal

TREATMENT

Carbarsone, 0 25 Gm b i d , for ten days and chiniofon in large doses, 3 tablets t i d , for seven days are recommended

The prognosis of balantidiasis is favorable except in emaciated patients

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Microfilariae in the Suspected Onchocercoma—The onchocercoma should be punctured the contents aspirated and then immediately examined on a slide with a cover glass It is possible to find numerous microfilariae but it is also possible that the investigation will give negative results if only adult parasites are present or if the adult parasites are of the same sex or if they are dead

Discovery of Microfilariae in the Eye—With the biomicroscope it is possible to see the microfilariae in the anterior chamber of the eye They appear as *very minute thread like bodies thin and refractive moving incessantly* and frequently escaping from the field of observation

Pathologic Findings in the Lesions—Pathologic findings in the lesions are so valuable that alone they are able to confirm the diagnosis

Peripheral Blood—There is usually a marked eosinophilia present



Fig 286—The author's technic of pressure by forceps and piercing with needle

Other Findings.—The complement fixation reactions of Gutierrez Villegas (1931) and others the cutaneous allergic reactions discussed by Hoffmann *and Vargas (1931) Mazzotti and Osorio (1943) and Wright and Murdock* (1944) the investigation for microfilariae in the spinal fluid and the erythrocytic sedimentation test of Linzenmeier have not proved to be of value in the diagnosis of onchocerciasis

PROGNOSIS

Onchocerciasis is not a fatal disease Its seriousness consists of the possibility of blindness from atrophy of the eyeball or of a secondary glaucoma However the regular surgical removal of the onchocercoma as well as careful search of the substances which elude ordinary exploration and future removal of them has reduced the number of onchocercal patients

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Plasmodium Vivax (Grassi and Feletti 1890)

These parasites in the initial stages are tiny organisms, usually containing a chromatin granule In most cases only one parasite can be found in each parasitized red cell although at times there may be more—occasionally as



Fig 26—Stomach of the mosquito with oöcysts of *Plasmodium vivax* Delafield hematoxylin stain. (×3 000) (Original photomicrograph of L. Beltrán.)

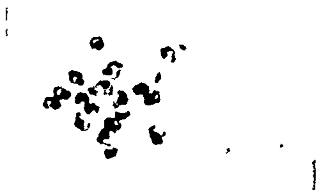


Fig 27—Merozoites of *Plasmodium vivax* Giemsa stain (×3 000) (Original photograph of L. Beltrán)

many as six in one erythrocyte The parasite soon begins to grow assuming an irregular ameboid shape and moves rapidly within the cellular stroma The name *vivax* is given to this species because of the vivacity of its move

CHAPTER 5

PLASMODIA OF MAN AND ANIMALS

ENRIQUE BELTRÁN

HISTORY

In 1880 Laveran, in Algiers, found in the blood of patients with malaria parasites which he considered to be the cause of the disease and which today are included in the order Haemosporidia, of the class Sporozoa, in the genus *Plasmodium*

Almost simultaneously with Laveran, Danilewski (1885), a Russian investigator, found in the blood of birds parasites that were very similar to those discovered by the French investigator, some of which today are considered as belonging to this same genus Plasmodium

Koch (1898) shortly afterward found similar parasites in the blood of monkeys

Last, Wenyon in 1908 (1926) and Aragao and Neiva (1909), independently in the same year, 1908 1909, found that reptiles also could be parasitized by Plasmodia

It is now known that parasites of the genus *Plasmodium* exist in various vertebrates, including mammals, birds, and reptiles

PLASMODIA OF MAN

Although Laveran had noted the entire asexual cycle of the parasite, it remained for Golgi (1889) to describe the different stages, thus establishing its relationship to the clinical manifestations of the disease

Due to the work of Ross (1895, 1898) in India and of Grassi, Bignami, and Bastianelli (1899) in Italy, it was soon established that the anopheline mosquitoes transmit this disease to human beings

The species generally accepted at present are
Plasmodium vivax (Grassi and Feletti, 1890),
Plasmodium malariae (Grassi and Feletti, 1890),
Plasmodium falciparum (Welch, 1897),
Plasmodium ovale (Stephens, 1922)

There is also lack of agreement concerning the proper designation of the genera and species of plasmodia which are found in man The problem is still under discussion (Coatney and Young, 1941, Sabrosky and Usinger, 1944, Beltrán, 1944) The designations given above have been accepted, according to International Rules on Zoological Nomenclature.

These plasmodia require two hosts One phase, the asexual, occurs in human blood, while the second phase, the sexual, takes place in the mosquito The four species present such marked uniformity in their life cycles that we can describe this cycle in general terms.

Infection in man begins with inoculation of sporozoites from the saliva of an infected mosquito For a long time the statement of Schaudinn (1903) was accepted that the sporozoite, after inoculation into the blood, penetrated directly into an erythrocyte, there it assumed the form that is typical of young trophozoites Schaudinn's observations could not be confirmed by other authors Moreover, it was proved that, from the time of inoculation by the mosquito to the first appearance of the forms which attack the red cells, there is a period during which no parasites can be observed microscopically and that the blood is not infective when inoculated experimentally into susceptible subjects

Fig 29—*Plasmodium falciparum*, blood smear Giemsa stain. *1*, young trophozoite [illegible]



Fig 30—*Plasmodium ovale*, growing schizont (Original photomicrograph of O Felsenfeld

ments When it attains its full growth there appear within it golden colored granules, these are spherical or rod shaped bodies These bodies are at first distributed uniformly throughout the parasite later they tend to become grouped into one central mass

Characteristic of this species is the increase in size of the parasitized red cells the cytoplasm becoming filled with dark red granulations These are called *Schuffner dots* They are considered one of the important diagnostic characteristics of this species

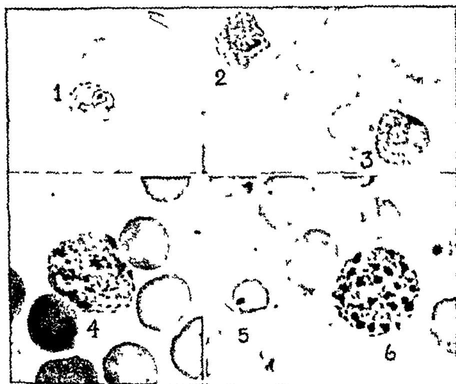


Fig 28 — [illegible] with Schüffner [illegible] young ring [illegible] with numerous [illegible] parasites note [illegible] *Hasnuevo* in *Le*[illegible] Medical Protozoology)

The trophozoite develops into a schizont and then into the segmented form usually with twelve to twenty four merozoites In Mexican strains of parasites (Beltran and Villasana 1945) the average number of merozoites is fourteen to sixteen

The schizogonous cycle of this species usually requires about forty eight hours a fact which explains the febrile attacks every third day However in double infections or because of lack of synchronization of one of the generations of the parasites there often can be observed a daily febrile reaction

The gametocytes are *round, but small, and of darker color, especially the macrogametocytes which are stained an intense blue*

The asexual cycle of this species usually requires seventy two hours which explains the periodicity of this type of intermittent fever, called *quartan fever*

Plasmodium Falciparum (Welch, 1897)

With *some exceptions, young forms alone are found in the peripheral* blood, these correspond to the ring forms or to young trophozoites At times *as many as six ring forms of the parasite may be found in a single erythro* cyte The schizonts *and segmented forms are localized in the visceral* circula tion The rings are usually smaller than those of the other two species, they frequently have two chromatin granules and are found in normal sized eryth rocytes, usually near the periphery

TABLE VI MORPHOLOGY OF PARASITES IN THICK BLOOD FILMS
(Courtesy of J W Colvin)

	Forms Present
Plasmodium vivax	All stages of development
Plasmodium malariae	All stages of development
Plasmodium falciparum	Only rings or rings and crescents

The Young Trophozoites (Least Diagnostic)

Growing and Large Trophozoites

P vivax—Abundant masses and blobs of light blue cytoplasm connected by threads or not visibly connected arranged in "Y" forms or triangles ameboid activity re flected older forms with fine yellow brown pigment, irregular, chromatin round or irregular

P malariae—Single blob of deep staining cytoplasm compact and close to nucleus, usually rounded or band forms, older forms chromatin may be obscured by crowding cytoplasm or elongated, heavily pigmented dark brown to black coarse granules

P falciparum—*Very much like young vivax* possibly more compact may still show double dot forms occasionally pigmented

Schizonts

P vivax—Chromatin masses irregular in contour in immature forms, 12 or more nuclei *in older forms* pigmented clumps

P malariae—Pigment more abundant 12 or less nuclei in *older forms, characteristic* arrangement in "rosette" or "daisy" pattern

P falciparum—Rarely seen, small both in size of parasite and size of nuclei, pigment dark to black

Gametocytes have a crescent shaped form with the nucleus and pigment near the center *The peculiarity of shape of the gametocyte distinguishes this* species from *others found in man*

The time required to complete the asexual cycle or schizogony is ap proximately forty eight hours as with *P vivax*, but there is generally marked

A characteristic of this species is observed in the merozoites which show marked preference for young erythrocytes or reticulocytes a phenomenon first noted by Craig in 1920 We have been able to verify this (Beltran 1941 Beltran and Sandoval 1945)

Gametocytes are round and relatively large and are easily identified by the enlargement of the erythrocytes in which they are found The gametocytes take a more delicate color than do those of *Plasmodium malariae*

TABLE V MORPHOLOGY OF MALARIAL PARASITES IN THIN BLOOD FILMS
(Courtesy of J W Colvin)

	P VIVAX	P MALARIAE	P FALCIPARUM
Color of cytoplasm	Light blue	Deep blue	Blue
Color of pigment	Yellow to brown	Black	Brown to black
Young Trophozoites			
Form	Small and large rings	Small compact rings	Small, delicate rings
Chromatin	Usually one dot	Large single dot	Often double dots
Pigment	None	Absent or fine	None
Growing Trophozoites			
Form	Irregular contour	Oval or bands	Rings
Chromatin	A dot or thread	A dot or thread	Often double dots
Pigment	Fine granules	Coarse granules	Scanty granules
The Infected Blood Cell			
Appearance	*Enlarged, pale*	*Normal*	*Usually normal*
Stippling	Schüffner dots	None	Maurer dots
Multiple parasites	Common	Rare	Very common
Growing Schizonts			
Form	Irregular contour	Compact, oval or round	Rarely seen resemble *P malariae*
Chromatin	2 to 10 granules	2 to 6 granules	2 to 8 small clumps
Pigment	Fine granules or clumps	Coarse granules or clumps	Fine granules or a single mass
Mature Schizonts			
Merozoites	12 to 24 in two rings or irregular	6 to 12 single ring or cluster	8 to 32 in two rings or irregular small
Pigment	Excentric mass	Central mass	Single dark mass
Shape of Gametocytes	Round or slightly ovoid larger than the red cell	Round or slightly oval same size as red cell	Crescent or sausage shaped
Pigment of Gametocytes	Scattered	Clumped	Centralized

Plasmodium Malariae (Grassi and Feletti 1890)

The general appearance of the parasite in the various stages is similar to that of *P vivax* There are however marked differences

The ring forms are difficult to differentiate from those of *P vivax* The mature trophozoites frequently show elongated forms which extend across the erythrocyte as a band There is no alteration in the size of the parasitized red cell *The pigment is composed of dark irregular granules There are no* Schüffner dots In preparations of *P malariae* it is not rare to find some erythrocytes containing the so-called Ziemann stippling which are also reddish but with poorly defined outlines appearing only in few cells of normal size

The merozoites are somewhat larger than those of *P vivax* there are usually six to twelve of them formed the average being eight

pecies may be experimentally transmitted to the canary, *Serinus canarius* Those which are most extensively found and which have been used most frequently in the laboratory are *P cathemerium* *P relictum* and *P circumflexum* the canary being used generally as the experimental host

Wolfson (1938) inoculated the domestic duck with *P cathemerium* Later, *P lophurae* was also used in ducks and in chickens Brumpt's *P gallinaceum* (1935), a parasite of domestic poultry is very favorable for experimental study Versiani and Furtado Gomes (1941) found in Brazil a new species which infects the domestic hen, *P juxtanucleare* This species was found almost simultaneously by us in Huixtla, (Beltrán, 1941a)

FORMS RELATED TO PLASMODIA

There exist in man and in animals certain forms of parasites which in some ways may be considered related to the plasmodia

The genus Toxoplasma is relatively common in guinea pigs Some cases of toxoplasmosis have been reported in man especially in children

There are in birds intraerythrocytic parasites, related to Plasmodium, belonging to the genus Haemoproteus There also exists in birds a parasite of the white blood cells belonging to the genus Leucocytozoon

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lack of synchronization of generations, with the result that the febrile reactions, which coincide with segmentation are irregular The number of merozoites is also quite variable, from eight to thirty six, with a tendency to the higher figures

Because of the morphologic and physiologic differences between this species and the other species of human plasmodia some authors believe that it should be placed in a distinct genus which they would call *Laverania* However, taking into acount the existence of intermediate forms in animal plasmodia most investigators do not follow this suggestion but prefer to retain *this parasite in the genus Plasmodium*

Plasmodium Ovale (Stephens 1922)

This is the rarest malarial parasite found in nature It is found in the Eastern Hemisphere cases have also been found in the Western Hemisphere The number of reported cases is still very small

The parasitized red blood cells are oval shaped (hence the name) contain many granules and take on a peculiar greenish hue In other respects the parasite follows the development of *P vivax* and *P malariae*



Fig 31 —Toxoplasma Smear from the brain of an infant. (Original photomicrograph of O Felsenfeld)

PLASMODIA OF ANIMALS

Plasmodia of mammals especially of the higher apes, have been used in the study of problems pertaining to pathologic anatomy and immunity in man Those most frequently used are *P knowlesi P inui* and *P kochi* found in Old World monkeys, and readily transmitted to *Macaca rhesus* the common laboratory monkey In the Western Hemisphere, *P brasilianum* a parasitic species found in the genus Alouatta has been used extensively

Plasmodia found in reptiles although they have been known for a long time, have aroused relatively little interest Thomson and Huff (1944), however, have again demonstrated the importance which reptilian plasmodia may have for chemotherapy and other research

The most important plasmodia found in animals and the most readily adaptable to experimental studies are those of birds As pointed out by Hewitt (1940) more than a dozen

CHAPTER 6

MALARIA

JOSEPH WESLEY COLVIN

Malaria (Italian colloquialism meaning "bad air") is a disease which is widespread throughout the world and endemic in a universal band bounded by latitudes of approximately 40 degrees north and 40 degrees south but epidemic far wider. It is produced by several species of the class Sporozoa in the phylum Protozoa and is characterized by its recurring periodic fever, debilitation and chronicity. Few diseases have had as extensive investigation as has malaria and writings concerning it extend back to Hippocrates and into lost antiquity. Certainly few diseases have touched its mark of cost to mankind. Malaria probably has a role in two million deaths annually and presents itself as a salient problem to medical minds each century. This in part is due to its prevalence, character and the elements involved in its transmission from man to mosquito to man. There are areas where strict vigil and earnest long untiring labor have been rewarded by the reduction or almost complete eradication of malaria as a health and economic problem. This has been done by breaking the links of the chain in the mechanics of its transmission.

CAUSATIVE AGENTS

The malarial parasites have been discussed in Chapter 5 and the description will not be repeated here.

Clinical observations of variations in species, virulence, infectivity and recurrences have led to the recognition of strains of plasmodia. These characteristics are apparently unrelated to the structural findings in the parasite.

Some strains under observation in the United States have been designated as follows (Coatney and Young 1941, Boyd 1945):

PLASMODIUM VIVAX	PLASMODIUM MALARIAE	PLASMODIUM FALCIPARUM
McCoy	Jones	Spears
Cleveland		Long
St. Elizabeth		Coker
U. S. Public Health		Costa
New Guinea Chesson		Thomas
Solomons		Perkins
		Cuban
		Mexican
		Panamanian
		Bynum
		Trinidad

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PLATE I —CYCLE OF DEVELOPMENT OF MALARIAL PARASITES IN MAN AND MOSQUITO

1 Bite of mosquito Injecting sporozoite into man from its salivary gland
2 14, 2A 15A, 2B 12B Blood stream of man
15 Bite of mosquito Receiving sexual forms from man
16 21 Stomach of mosquito Oocysts formed on the outer wall of the mosquito's stomach
25 Salivary gland of mosquito
2 2A, 2B Free sporozoites
3 3A 3B Penetration of sporozoite into a parenchyma cell of the liver
4 4A, 4B Beginning schizogony Ring form
2 9, 4A 10A, 4B 7B Schizogony Cause of fever
5, 5A, 5B Half grown parasite
6, 6A Mature parasite
7, 7A, 8A Beginning division
8, 9A, 6B Division forms
9, 10A, 7B Merozoites
10, 11A, 8B Young male
11, 12A, 9B Adult male
12, 13A, 10B Young female
13, 14A, 11B Adult female
15 Bite of mosquito Inoculation of mosquito from patient
16 Macrogametocyte
17 Microgametocyte
18 *Fertilization*
19 Zygote
20 Ookinete entering stomach wall
21 Young cyst on outer stomach wall
22 Cyst with sporoblasts
23 Cyst with sporozoites
24 Wandering sporozoites
25 Sporozoites in salivary gland of mosquito

TABLE VII OBSERVATIONS ON TWO STRAINS OF VIVAX MALARIA
(From Swellengrebel and DeBeck 1938)

NAME	PARASITEMIA WITHOUT SYMPTOMS (%)	LATENCY PERIOD (DAYS)	DAILY FEVER (%)	HIGH FEVER (%)	SPONTANEOUS RECOVERY (%)	RELAPSES (%)
Holland	38	21	19	8	10	10
Madagascar	7	12	80	30	0	80

These are or have been used in the therapeutic induction of malaria for paretic patients Interesting racial resistance has been found especially in Negroes toward *vivax* infections Some workers have felt that Caucasians too in selected cases have exhibited a similar resistance James divides them into three groups very susceptible refractory and between these limits with a majority falling in the middle group In the treatment of paretic patients if one strain does not produce a malarial take a different strain is used Success is more likely to occur with a different species entirely though similar gradations of resistance have been reported in all species (James 1937 *vivax* and *falciparum* Sinton Hutton Shute 1939 with *ovale*) Boyd succeeded in inoculating 100 per cent of his patients on the second try with *P vivax* and felt that it was unsuccessful the first time because of parasitic alterations rather than the individual patients

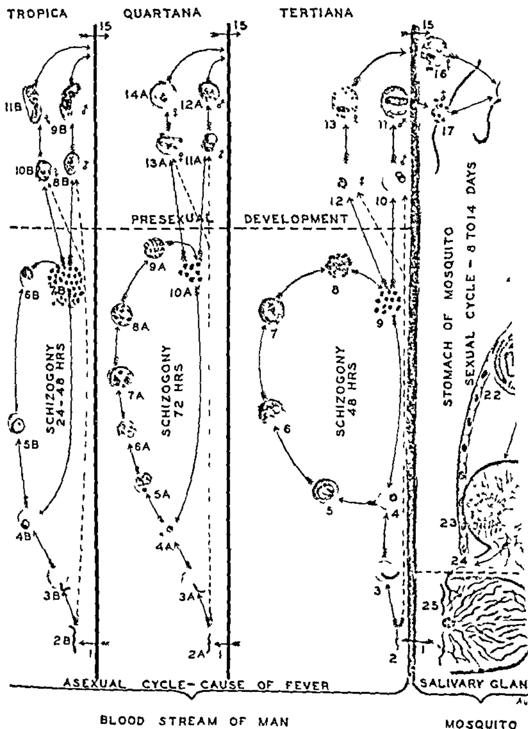
VECTORS

See Chapter 7

PATHOLOGY

Malaria produces extensive physiologic and histologic changes accompanied by a multiplicity of significant pathology The reticuloendothelial system probably bears the brunt of the initial attack only to be taxed later with toxic by products and cellular debris during erythrocytic invasion The function and existence of red blood cells are destroyed by parasitism with a resulting state of toxicity whereby other nonparasitized normal erythrocytes may be destroyed by lysis The release of blood pigment from red cells in itself causes enough disturbance to disrupt hematopoietic balance to say little of other disruptions incident to protozoan infection Many events occur in pathologic sequence before onset of the varied anemic states induced by the increased destruction of red blood cells These are the poignant manifestations of the so called blood organs those with sinusoids liver spleen bone marrow etc Clark (1928) indicated that parasites have a tendency to localize in these places and pointed out that this might be a defense action on the part of the body This resultant centralizing of parasites causes retardation of blood passage and enlargement of the organs involved so that splenomegaly and hepatomegaly are features of the disease when fully developed in the host The pathologic response is one of hyperplasia hypertrophy and pigmentation

CYCLE OF DEVELOPMENT OF MALARIAL PARASITE IN MAN AND MOSQUITO



The white blood picture in malarious infections changes from one of normal tenure to one of reduced white blood count leucopenia. This is reversed somewhat during the paroxysms and then decreases. Persistent malarial latency found in *P vivax* and *malariae* usually brings about an increase in large mononuclear leucocytes. The picture is therefore one of leucopenia with a later absolute mononuclear leucocyte increase. The same in general applies to *P falciparum* infections this species is not as refractory to treatment as the other two species. Thus there is no degree of latency.

	RED CELL PREDILECTION	PARASITIC RANGE (USUALLY)
Plasmodium vivax	Reticulocytes	8 000 to 20 000 per c mm
Plasmodium malariae	Mature red blood cells	Up to 10 000 per c mm
Plasmodium falciparum	All age cells	Up to 500 000 per c mm

Thus it can be seen that somewhat of a limitation is imposed on the first two whereas with the last practically no limit exists in untreated cases implying a much graver prognosis.

The common pathologic course of benign tertian and quartan malaria is not one of severity but rather one of extensive mildness in which there apparently occurs a balance between the disease and resistive body forces. Undoubtedly there is interplay between body immunity to a species after a time and the invasive powers of the infective species. One apparently becomes weak and the other stronger for the moment only to reverse later.

Prolonged infection sees the exacerbations becoming farther and farther apart with these two species. That the threshold level of clinical manifestation of the disease is raised is evidenced by the fact that so many asymptomatic parasitemias are found in endemic areas. The adaptation of the body to the malarial toxins via immunity or histologic compensation or subsidence of virulence of the species, or all these factors may explain this. The consistency of the pathologic picture in most cases suggests that the time element of change is prolonged so that the whole scheme develops more slowly with a balance occurring between the toxicity and destructiveness of the parasite and the ability of the host to compensate for the invasion and to live compatibly with it.

CLINICAL SYMPTOMS

Paroxysms—Typical

The clinical observations of malaria in the past have led to the common naming of the various species causing it. These are in rather prominent usage today although it is less confusing to use the generic terms such as *P vivax* etc. The clinical terms are respectively benign *tertian quartan* and *malignant tertian or subtertian* malaria. Tertian is derived from the Latin meaning three being applied to *vivax* malaria the chills and fever occurring on the third day. Quartan comes from the Latin meaning four being applied to *malariae* malaria the paroxysms occurring on the fourth day. In each instance the first day is a day of chill and fever in *vivax* and *ovale* and

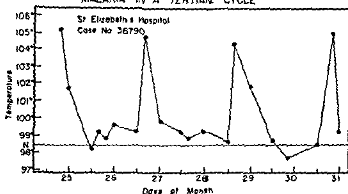
The spleen and liver in an acute case of malaria are congested enlarged soft and spongy with a dark color The more chronic the case the darker and firmer the consistency The continuous hyperplastic changes which occur in capsular fibers and internal corpuscular tissue elements bring this about The spleen and liver are often three to four times their normal size, with a blackish cast in patients dead of long standing malaria Capillary thrombosis and hemorrhages even moderately larger infarctions have been found to occur

Microscopically highly pigmented cells cloudy swelling and necrotic foci are observed in the liver The phagocytes monocytes and reticuloendothelial cells are heavily darkened with black pigment Vacuolization toxic changes and fatty infiltration all may occur as complications There may be found what is called ring hemorrhages for example capillaries plugged with parasitized red cells and edema in the brain with subsequent development of malarial granulomas Those induced by vascular thromboses are not confined locally but may be widespread over the body occurring in the heart which shows focal or interstitial myocarditis in the nephritic tubular areas pancreas thyroid lungs and suprarenals all usually appearing in fatal cases Focal necrosis and petechial hemorrhage in the gastrointestinal tract are not rare

Acute stages of malaria produce a drop in blood protein and reversal of A/G ratio Blood viscosity is changed and water balance disturbed The effect of these on kidney secretion may cause retention of by products of body metabolism

The overtaxation of the resistive forces of the body and the wholesale destruction of red blood cells by malaria have brought in association to it a clinical term describing a condition found in malarious areas called "black water fever" the pathology of this state being the same as that produced in malaria except that every finding is acutely intensified and the absence of kidney function typifies the clinical picture There occurs in this condition a vastly overwhelming loss of total red blood cells so much that one to two million may be destroyed in twenty four hours Death may ensue in a very short time The species identified most commonly with blackwater fever is *P falciparum* though recently a new malignant vivax strain occurring in children has been reported from Russia In these cases there was found a heavy hemoglobinuria

A state of cachexia will develop in long standing chronic malaria the result of the anemia and impaired function of vital organs needed to maintain good health Intervening intercurrent infection causes complete debilitation or even death There occurs in malignant malaria (*P falciparum*) a greater tendency for the parasitized red blood cells to clump or agglutinate together than is evidenced by quartan (*P malariae*) or benign tertian (*P vivax*) This was observed many years ago in the brain and other organs after death Cropper (1908) found this agglutination in the peripheral blood stream before death Knisely (1941) thought the red blood cell agglutination was in liver passage phagocytized there


MALARIA IN A TERTIAN CYCLE
St Elizabeth's Hospital
Case No 36790
106°
105°
104°
103°
102°
101°
100°
99°
N
98°
97°
Temperature
25
26
27
28
29
30
31
Days of Month

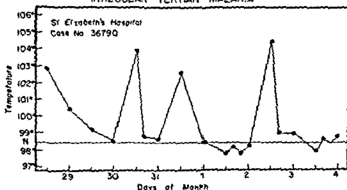
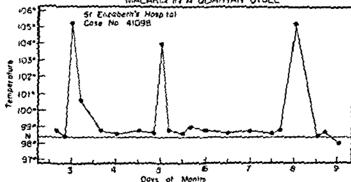
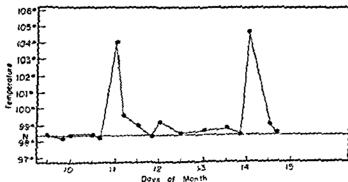

IRREGULAR TERTIAN MALARIA
St Elizabeth's Hospital
Case No 36790
106°
105°
104°
103°
102°
101°
100°
99°
N
98°
97°
Temperature
29
30
31
1
2
3
4
Days of Month

Fig. 33.


MALARIA IN A QUARTAN CYCLE
St Elizabeth's Hospital
Case No 41098
106°
105°
104°
103°
102°
101°
100°
99°
N
98°
97°
Temperature
3
4
5
6
7
8
9
Days of Month


106°
105°
104°
103°
102°
101°
100°
99°
N
98°
97°
Temperature
10
11
12
13
14
15
Days of Month

irregularly so with *falciparum* malaria, the next chill is forty eight hours later or on the third day The same applies to *malariae* malaria the time interval "Benign" and l outcome of the ated with it the mortality and pathology of the seemingly mild *falciparum malaria* which became known as "malignant tertian" malaria

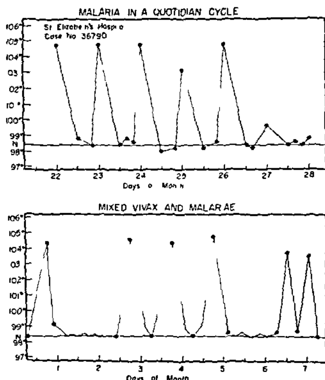


*Fig 3**

The chill fever sweat periodic syndrome is called a paroxysm and varies in length and periodicity with the species The *vivax* and *malariae* paroxysms exhibit variability but occur approximately four to ten hours from the beginning to the end *Falciparum paroxysms are somewhat milder but last upward to* from ten to even thirty six hours In the former two the temperature usually falls to normal or below normal and is considered intermittent whereas in the latter the temperature may not come down to normal but rather remains above it hence it is considered a remittent type and persists longer The typical paroxysm consists of a preceding cold phase (chill) lasting from one half to one hour during which the patient is pale erector pilae spasm is prominent, coarse tremors are evident and a sense of anxiety is obvious The body temperature rises and chilly sensations of wave character pass over the body This is followed by *outright severe tremors and local spasms and chattering of the teeth,*

symptomatology and signs of dilated right sided heart These are found usually at high altitudes connected with a fatty degeneration of the myocardium The *bronchopneumonic* type has symptoms referable to that body area

The subjective experience in clinical *vivax* malaria is usually more harassing than with the others First the prodromal symptoms such as rheumatoid pains etc precede a sudden onset of paroxysm all of which are a severe stress for the patient These may have a *periodicity* *For the most part the* paroxysm even if somewhat irregular at the start and which may be daily in occurrence always becomes fixed on a forty eight hour recurrent basis Between attacks patients *feel well being able to do their work*

P malariae infection has had associated with it a tendency to some nephritic involvement as a complication Untreated *vivax* malaria and *malariae* infection will by nature of the cell selectivity of the parasite become limited over a period of time whereas *falciparum* malaria on the same basis may exhibit no such limitation

	PARASITES PER C MM	(MAX)	PERIOD COVERED
Plasmodium vivax	20 000 to 40 000	50 000	2 to 3 yr
Plasmodium malariae	5 000 to 10 000	20 000	7 to 10 yr
Plasmodium falciparum	Unpredictable	No limit	2 to 6 mo

Although the incubation period of naturally acquired malaria is approximately *fourteen days that of artificially transmitted malaria is shorter eleven* days (James 1931) Latency is a prominent feature of both *vivax* and *malariae* The initiation of the paroxysm is dependent upon the rupture of the mature schizonts Manson Bahr (1945) has suggested that the syndrome is of the nature of allergy The manifestations of a *relatively nonimmune group* exposed to malarial infection have been observed in the recent war years The latency exhibited by *vivax* even though cases were treated adequately plus thorough drug supervision preceding entrance into endemic areas has *caused considerable* discussion At this point exacerbations are not as frequent as previously This leads one to suspect some resistance is developing as time passes which may or may not be the case but is probable The *paroxysms are apparently* as severe as previously only *less frequent* Few, if any cases of the severe *falciparum* malaria developed since adequate suppressive doses produce successful results

The incidence of multiple infections is *not as uncommon as one would* imagine and when occurring may present an unusual picture The presence of two groups of *vivax* or *malariae* in a patient will ofttimes present a more frequent rise of temperature *(quotidian malaria) until the development of the* schizonts becomes more synchronous as they will tend to do in similar species infection This is as yet inadequately explained Infection by heterogeneous species will usually end with one or the other dominating the clinical picture *for example* if *vivax* and *falciparum* are found the latter, having a subtertian *cycle and attacking* any type cell may dominate in untreated cases If *vivax* and *malariae* are found it is reasonable to suppose that the *vivax* will eventually *dominate* being of the shorter cycle though the extreme latency of quartan will become *evident later* *In this* last incidence the patient would have fever

with a harassed, pinched appearance to the face which may appear to have a bluish cast An attempt is made to keep warm by using any or all means at hand The effect of this varies with individuals some requiring bed rest with almost collapse supportive measures and some at the other extreme proceeding with their work though obviously seriously hampered The mind remains clear if not actually more alert than usual The pulse is increased and respiratory rate is increased but is more shallow The desire for frequent micturition is strong and any attempt to eat may be followed by nausea and vomiting This stage is followed by the hot or flushed phase The face is flushed eyes bright, the body has a red appearance There is a sense of relief attendant to the ending of the cold stage only to be followed by the aggravation of pyrexial symptoms of the hot stage for example headache becomes worse and a feeling of abdominal tenseness around the splenic area may be experienced It is not uncommon to find herpetic lesions around the mouth and nose This stage with a temperature of 104 to 106° F may last three to four hours before the final stage of the paroxysm starts that of sweating The skin previously dry and hot becomes moist and cool The temperature falls rather rapidly and perspiration starts about the head spreads over the body and becomes quite profuse lasting two to three hours Accompanying the temperature fall is a feeling of exhaustion and sleep soon intervenes In the course of a few hours the patient awakens feeling fresh but not free of fatigue The patient is usually well until the initiation of the next paroxysm

Paroxysms—Atypical

The foregoing description of a typical paroxysm is almost invariably associated with the *vivax* and *malariae* species the benign tertian and quartan malaria respectively also with *P ovale* except that with this species the clinical manifestations are somewhat milder The atypical paroxysm can occur in individuals in mild forms producing malarial low grade fever headache and rheumatoid pains in the joints long bones and muscles The symptoms are much like those preceding the onset of a head cold These occur in apparently highly resistant patients or partially treated cases For the most part the atypical paroxysms are associated with malignant tertian subtertian or *falciparum* malaria In this type of malaria several clinical forms have become well known

First is the *algid form* thought to be due to localization of large numbers of parasitized red blood cells in the large and small blood vessels of the intestinal tract and abdominal organs The algid type is characterized by prostration bordering on shock with peripheral circulatory collapse and an associated high fever The patients may exhibit uncontrollable vomiting severe dysentery with bloody stools hemorrhage and purpura Consequently severe malaria is clinically designated according to the most prominent symptom or sign The aggregation of large numbers of parasitized red cells in the brain usually results in the *cerebral type* which features delirium coma meningismus aphasic or hemiplegic signs There are other types that have *cardiac*

and besides gastric disturbance anorexia etc there may occur tendencies to hemorrhage There may be a Banti like syndrome in the picture of cachexia The skin will ulcerate easily from abrasions etc *As in many chronic illnesses* the true character is overshadowed by subsequent developing conditions such as deficiency polyneuritis paralyses amblyopia etc The mental depression deterioration of memory and lack of concentration powers that have been associated with malaria infections and malarial debility have been found rarely if at all in Service developed cases of malaria during World War II

General Considerations

Through the many years of observation on malaria several factors have been associated as being incident to the relapses of malaria clinically How these operate is obscure and open to scientific criticism but the dictates of good judgment and common sense place them in close proximity to recurrences of clinical exacerbations of latent and relapsing malaria These factors are overindulgence in alcoholic beverages *undue exposure to elements fatigue* shock surgical procedures childbirth etc Many authorities believe these to be contributing factors in the cause of recurrent malaria

Malariae (quartan) *is considered the worst offender in this regard* especially in view of the many years this species will persist The patient is usually symptomless and the parasites undiscoverable in blood and in the organs though obviously *they* are garnered somewhere in *the body only to* produce relapses when the conditions are right These relapse periods vary in artificially induced malaria and the naturally acquired ofttimes terminating spontaneously in the former (Boyd and Kitchen 1937) Much emphasis has been placed on the relapses occurring in Service acquired *vivax* malaria Since the relapses happen frequently they may constitute an economic burden *on* the patient in his usual pursuits However quartan malaria relapses run into many years benign *vivax* is not expected to do this

The question naturally arises *what influence does the malarial disease* have on other conditions? The transmission of malaria *congenitally is yet an* open question There are incidences where the malarial parasites have been found in the newborn but in some *there* has been *some abnormality connected* either with intrauterine life or with parturition When fetal infection does occur it *must* place a severe burden on the child There are other cases where it appears that congenital infection has no doubt occurred *most likely via* the placental route (James Brown Tanner Hewitt) Clark (1928) on the other hand has made extensive surveys with this point in mind and found no crossover to fetal blood of parasites even though the mother was heavily infected Treatment of this is discussed under Therapeusis There are many *cases reported and on record* of malarial infections developing from the transfusion of blood from a donor who has an asymptomatic malaria *or who has* had history of previous infection The interval of time between *clinical malaria in the donor* and the transfusion time to the new case has been as long as several decades The species involved has usually been *P malariae*

twelve days in nineteen Perhaps there would be a double rise in temperature on the seventh thirteenth and nineteenth days as *vivax* and *ovale* produce chills every forty eight hours and *malariae* every seventy two hours *Falciparum* produces them irregularly from approximately thirty six hours onward The symptoms are mild almost insidious until the more severe clinical malaria occurs Table VIII represents clinical symptomatic differences

TABLE VIII

	TERTIAN	QUARTAN AND SUBTERTIAN
Seriousness	Nonkilling	Killing
Distribution	Global but spotty	Tropical
Symptomatology	Severe	Milder (insidious)
Course	Regular	Irregular
Relapses	Prone	Less so
Latency	Four plus	Minus
Treatment	Resistant	Susceptible
Prognosis	Good	Guarded

Malarial Debility

The repetition of attacks of any of the malarial species if untreated or inadequately treated may lead to serious debility in physical and mental capacities Here greatly enlarged livers and especially spleens are observed

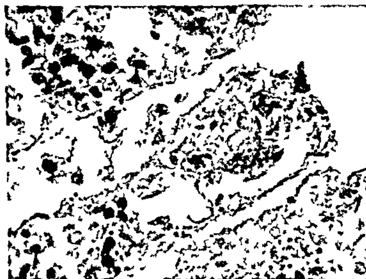


Fig 15 —Malarial intestine (Original photomicrograph of O Felsenfeld.)

The skin is a sallow color the turgor is gone the face is pinched and the ocular sclera is a yellowish color A pot bellied ' type abdomen is found especially in children Growth impairment may be obvious The over all resistance to minor ailments is drastically lowered by the chronic anemia Patients with the more severe type may show ascites and edema of the legs

bite fever or Haverhill fever should be thought of diagnostically In the latter areas add kala azar trypanosomiasis Weil's disease and especially amebic liver abscesses

Endocarditis usually follows some acute infectious process as a complication blood cultures and evidences of bacteriemia irregular periodicity to the daily temperature rise heart murmur help in differentiating it

An exhaustive careful study will perhaps be the best method of ruling out tuberculosis The absence of typical paroxysms and crises, a positive lung x ray *cough hemoptysis and an unexplained moderate polycythemia* are suggestive of tuberculous splenitis Pyelitis usually has symptomatology referable to the urogenital system In early cases only bacteria and some pus may be found as an abnormality in the urine Typhoid fever is apparently easy or difficult to differentiate outstanding features are slow pulse increasing fever each day history of exposure *blood culture early in the disease Urine culture later* or the Widal test is of help Relapsing fever can usually be ruled out using blood smears and finding the causative spirochete during the fever An atypical typhoid type of tularemia can be confusing The lack of positive blood smears for malaria and the use of blood agglutinins for specific tests in the second week will rule out tularemia Foshay's intradermal antigen is considered specific in tularemia Influenza can be ruled out by blood smear examination and absence of catarrhal symptoms Brucellosis can be established by blood culture and by suggestive skin tests read in forty eight hours the presence of agglutinins and the opsonocytophagic index Ratbite fever usually can be determined by dark field or blood smear examination or lymph node puncture, there are usually lymphangitic signs and regional adenopathy in the proximity of the original ratbite Animal inoculation into mice or guinea pigs can be used to differentiate from malaria

Kala azar is in its onset in some cases similar to malaria though a double daily rise in temperature has been found in some areas The finding of *Leishman Donovan bodies by liver or splenic puncture* or using blood to culture the causative Leishmania can usually aid in differentiating this disease from malaria Trypanosomiasis both the African and South American types can be identified by finding the parasites in the blood during the acute phase Winterbottom's sign glandular enlargement in the neck together with finding the parasite are reliable in establishing a diagnosis of African trypanosomiasis Gland puncture is not considered very reliable in Chagas' disease (South American trypanosomiasis)

Weil's disease *caused by Leptospira icterohaemorrhagiae, has an abrupt onset in many cases* similar to the start of a malarial paroxysm It can be differentiated by using the blood smear to demonstrate the etiologic agent *during the first few days of the disease thereafter the organisms appear in* the urine Most effective is injecting blood into a guinea pig or hamster, *finding* the Leptospira and positive agglutination tests

Liver abscesses with periodic fever are in certain incidences difficult to differentiate from malaria The blood smears high polymorphonuclear leucocyte count or *antimalarial drug therapeutic* test may be the only reliable

This type of transmission and inoculation has been found also among drug addicts (Applebaum and Gelfand, 1934 Helpern 1934 Jolliffe 1940 and Most 1940)

There are several ways of determining the degree of malarial infection in a locality These means are by using the splenic index parasitic index sporozoite rate in salivary gland (mosquito) or by dissection of the mosquito stomach and observing oocysts All of these are not without fallibility and have their points of controversy The *splenic index* is the number of palpable spleens per 100 persons examined The *parasitic index* is the number of positive blood smears per 100 people The *sporozoite rate* is the number of positive mosquito salivary glands per 100 mosquitoes *Mosquito oocyst index* is the number of positive mosquitoes found per 100 mosquitoes examined The *endemic index* is the parasitic index plus the splenic index Somewhat of a criterion has been advocated on the degree of endemicity as follows

10% or below	Low endemicity
10 to 25%	Moderate endemicity
25 to 50%	High endemicity
50 to 90%	Hyperendemicity

Under natural conditions when the index is below 10 per cent the other 90 per cent must have either quiescent malaria or no malaria The thought has been suggested that this may be the type of situation where an increase in malaria could be expected on the basis of so many being more or less susceptible (Komp and Clark 1934)

DIAGNOSIS

The diagnosis of malaria rests on (1) positive blood smear (2) periodic fever and paroxysms or periodic symptoms (3) splenomegaly (4) history of malaria or of having been in an endemic area (5) the judicious ruling out of similar conditions producing a complicated malaria picture (6) the complement fixation test which has been found to be suggestive and apparently worth while in patients of a quiescent malarial phase (Coggeshall and Eaton 1938) (7) drug therapeutic tests with antimalarials (8) pigmented leucocytes in the presence of leucopenia with a relative increase of monocytes which is suggestive

DIFFERENTIAL DIAGNOSIS

Malaria can unfortunately simulate almost any disease consequently many other conditions must of necessity enter into the process of differentiation and the ascribing of a malarial state The geographic location of the case will afford some help in this If in a nontropical area the tropical diseases can be eliminated fairly easily from consideration they should be borne in mind if the patient has recently returned from the tropics If the patient is in a tropical area both temperate and tropical diseases must be considered. In the former area diseases such as septic states endocarditis tuberculosis pyelitis typhoid fever, relapsing fever tularemia influenza brucellosis rat

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measures in these cases.* Those abscesses due to *Endamoeba histolytica* can be identified by using what appears to be a significantly reliable test, the amebic complement fixation procedure.

Filariasis can be differentiated by unilateral swelling and adenopathy and by blood smear and serologic methods. Yellow fever has a more prolonged onset. Albuminuria occurs on the second or third day with mild jaundice, but blood smears will aid in establishing a diagnosis of malaria.

Chronic malaria and hookworm disease can be differentiated by laboratory methods: blood smears or finding the nematode eggs in the stools.

Blackwater Fever

For the purposes of complete understanding a few clinical points regarding this condition are included under this section. Blackwater fever associated with *falciparum* malaria is fortunately not too common. One Navy clinician who spent more than a decade in malarial areas saw only three cases in nine years in nonimmune individuals who had entered a *P. falciparum* endemic area and resided there for only a short while. The disease appeared with the swiftness of an allergic phenomenon and probably was not too far removed from a state of that character. The patient's malaria seemingly improves, and people native to the area apparently are not subject to the disease. However, natives going from one area to another, for example, elevated regions where one species, *quartan* or *vivax*, is dominant, to sea level areas where *falciparum* is present in great numbers, have fallen victim to blackwater fever. Age or sex seems to make no difference, and the occurrence of the disease tends to be familial in character. A recent suggestion has been offered by Butts (1945) regarding this familial tendency, namely, that the Rh factor may be instrumental in the hemolysis of blood cells in blackwater fever. Factors involved in its precipitation are varied and debatable. These few listed are some, but by no means all, of the factors discussed or considered:

1. Amount of exposure to malaria
2. Fatigue
3. Exposure to debilitating conditions
4. Alcoholic beverage excess
5. Quinine
6. Atabrine
7. Arsenicals
8. Plasmochin
9. Pregnancy
10. Biologic variation in individuals

The pathologic sequence of events can be succinctly summarized as:

1. Hemolysis of parasitized and normal red blood cells at the rate of over 1,000,000 in twenty-four hours
2. Development of hemoglobinuria
3. Early appearance of jaundice
4. Usually azuria. Maegraith (1945) advances the theory that this may be due to renal anoxia.

*Editor's note (O. F.): Paludrine and Chloroquine (Aralen), however, are active also against liver amebiasis.

6 Lobe of pronotum distinctly larger than the *mesonotum* 7
Lobe of the pronotum generally smaller than the mesonotum spiracular bristles present in *Psorophora* and *Theobaldia* fringe of squamula almost always complete Tribe *Culicini* (in part)
7 Spiracular bristles absent (*Haemagogus* *Aretmapodites*) Tribe *Culicini* (in part)
Spiracular bristles present (substituted by scales in *Limatus*) fringe of squamula generally absent or incomplete when present Tribe *Sabethini*
8. Scutellum slightly trilobate Genus *Chagasia*
Scutellum uniformly rounded 9
9 Stalk of the fourth vein undulant Genus *Bironella**
Stalk of the fourth vein straight Genus *Anopheles*

KEY TO ADULTS OF THE SUBGENERA OF AMERICAN ANOPHELES

1 Mesonotum with narrow median white fringe body without scales in the female the hairs of the antenna are as long as the width of the thorax all wing scales are black small mosquitoes *Stethomyia*
Mesonotum with two median longitudinal black bands and two dorsal stripes in the female the hairs of the antenna are not as long as the width of the thorax costa of the wing with four or five white spots alternating regularly with black spots abdomen without scales *Kerteszia*
Mesonotum and costa marked otherwise 2
2 Scales of the costa subcosta and first longitudinal are more abundant than in the rest of the wing forming a distinct contrast petiole of second marginal cell is one third to one half the length of this cell wings with scales of uniform coloring or only with light colored scales in the fringe of the apex *Coelodiazesis*
Abundant scales on all veins or with only the costa bearing the more abundant scales 3
3 The third fourth and fifth segments of the posterior tarsus entirely white or with narrow black rings these segments show different spots in the median anterior tarsus 4
The third fourth and fifth segments of the posterior tarsus entirely black or with narrow light spots 6
4 Abdomen with scales or bands of scales posterolaterally at least in the last segments 5
Abdomen pilose only the genital segment bearing scales sixth longitudinal wing vein with large black spots *Myzorhynchella*
5 Sixth longitudinal wing vein with small black spots near the extremities, wing scales not broadened *Nyssorhynchus*
Sixth longitudinal wing vein with numerous tiny spots with one outstanding central spot wing scales very broad *Shannoniella*†
6 Apical third of *posterior femur* covered with erect black scales, wings with white yellow and black scales *Lophopodomyia*
Apical third of posterior femur without erect black scales 7
7 Spotted aspect of wing due to grouping of some dark scales, *light scales only in the* apex of the costa first longitudinal and in the region corresponding to the fringe petiole of second marginal cell is 40 to 50 per cent of length of cell *Pussellia*
Wing with scales of uniform color which give a spotted appearance due to their grouping *without light-colored scales* in first longitudinal and with a petiole of second marginal cell which is more than 60 per cent of length *of cell* or wing with numerous light colored scales in various veins 8
8 Single proepisternal seta sixth vein *entirely* black or with only a small median spot *Arthuromyia*
Generally with more than *four proepisternal setae* sixth vein entirely black or having up to five black *spots* *Anopheles*

*Present only in New Guinea and adjacent islands
†The validity of this subgenus is doubtful

CHAPTER 7

MALARIA CARRYING MOSQUITOES AND THEIR CONTROL

Luis Vargas

INTRODUCTION

The classification of the anophelines most widely accepted by modern authors is that of Edwards (1932) which recognizes three genera Chagasia Bironella and Anopheles the last with three subgenera for the American species Stethomyia Anopheles and Nyssorhynchus Following the work of Edwards new additions have been made to the subgenera Vargas (1943) described Russellia

At the present time the subgenus Anopheles is represented in the New World by thirty one species divided into two groups Anopheles and Arribalzagia

In the following key to systematic classification the section referring to subfamilies and genera is taken from Edwards (1932) and the section referring to tribes is from Lane and Cerqueira (1942) with slight modification

KEY TO SUBFAMILIES AND TRIBES

1 Subcosta long extending to and reaching the costa, vein 1 with four branches, vein 2 bifurcated vein 3 simple cross vein 1—2 absent vein 4 bifurcated cross veins 3—4 and 4—5 present vein 5 bifurcated vein 6 long and following margin of the wing auxiliary vein absent or very diffuse (Family Culicidae 2
Without the above listed combination of characteristics other Diptera

2 Antenna with 14 segments subcosta terminating at or before base of vein 2 mouth parts short scales absent Subfamily *Dixinae*
Antenna with 13 segments subcosta terminating much beyond the base of vein 2 scales present 3

3 Mouth parts short palpi curved scales for the most part confined to margins of the wings Subfamily *Chaoborinae*
Mouth parts modified to form a long proboscis palpi not curved wing veins and legs bearing scales (Subfamily *Culicinae*) 4

4 First abdominal tergite without scales posterior coxa slightly shorter than the mesepimeron posterior margin of scutellum always rounded (slightly trilobate in *Chagasia*) palpus of female approximately the size of the proboscis (shorter in *Bironella*) squamula with complete fringe Tribe *Anophelini* 8
First abdominal tergite with at least one spot posterior coxa distinctly longer than the mesepimeron 5

5 Scutellum always rounded at the posterior margin palpus of female longer than the antenna rig 1 external half more slender, flexible curved back squama with fringe absent Tribe *Megarhinini*
Scutellum trilobate palpus of female much shorter than the proboscis flexible with external half not curved 6

SPECIES	BREEDING PLACES	DISTRIBUTION
claviger (*bifurcatus* Meigen, 1818) Meigen, 1804	In cisterns, shallow pools, water collections in rocks, in wells	Southern Europe, North Africa, Asia Minor, and Turkestan
fluviatilis James, 1902 (*listoni* Liston, 1901)	At the headwaters of piedmont streams, pools of water, in streams, springs, and drainage canals, at times in bends of marshes, in lakes and ponds	Turkestan
maculipennis labranchiae Falleroni, 1926 (*labranchiae atroparvus*) (*labranchiae labranchiae*)	In salt water of coastal marshes, in warm fresh water of rice fields, in highland streams, in sun or partial shade	Coasts of Dalmatia, Italy, Southern Spain, Sicily, Sardinia, Corsica, Northwest Africa
maculipennis messeae Falleroni, 1926	In sunny, cold and fresh, stagnant water, large rivers, lakes and marshes	From Norway and Sweden south to Italy, eastern Mediterranean, from British Isles to north shore of Black Sea, Asiatic Russia
maculipennis typicus Meigen, 1818	Fresh water, lowlands and hills	See *messeae*
pharoensis Theobald, 1901	In swamps, floodlands, and rice fields with much vegetation	Palestine, Egypt
sacharovi Favre, 1903 (*elutus* Edwards, 1921)	In sunny inland and coastal marshes, fresh or brackish, slow streams	Italy, Sardinia, the Balkans, Russia, Palestine, Iran, Iraq, North Africa, West China
sergenti (Theobald, 1907)	In rice fields, borrow pits, canals with slow current and dense vegetation, seepage water	Canary Islands, Algeria, Tunis, Egypt, Palestine, Syria
stephensi Liston, 1901	In wells, cisterns, flower pots, tile drains, and covered irrigation canals and other temporary water receptacles, especially in inhabited communities	Arabia, Iraq, Iran
superpictus Grassi, 1899	Standing pools, small streams, rivers and irrigation drains, generally in mountainous regions, prefers edges of water	Southern Europe, Southwest Asia
	Oriental Regions	
aconitus Donitz, 1902	Irrigation ditches, dams, reservoirs, ponds, rice fields, tide water, pools in river beds, ruts in roads	India, Ceylon, Burma, Siam, Indochina, Malaya, Sumatra, Java, Borneo
culicifacies Giles, 1901	Commonly in fresh, clear water, pools, borrow pits, farm wells, rocky or sandy river beds, rice fields, and occasionally in salt water	India, Burma, Ceylon, Siam, French Indochina, and southern Arabia
fluviatilis James, 1902 (*listoni* Liston, 1901)	See Paleoarctic region	India, Burma, Siam, French Indochina, Ceylon
hyrcanus Giles, 1900	Especially in rice fields, in stagnant water with vegetation, in canals, borrow pits, lakes, and stream banks	India, Ceylon, Burma, Siam, Indochina, China, Malaya, Sumatra, Java, the Philippines, Borneo, Iran
hyrcanus var. *sinensis* Wiedemann, 1828	Stagnant water in rice fields, marshes, and ponds and irrigation channels, sometimes along shores of streams and lakes	India, Burma, Indochina, China, Korea, Japan and Formosa, Netherlands East Indies

LIST OF THE ANOPHELES MORE IMPORTANT IN THE TRANSMISSION OF MALARIA

SPECIES	BREEDING PLACES	DISTRIBUTION
	Neoarctic Region*	
albimanus Wiedemann, 1821	In clear, sunny, stagnant, fresh or salt water	Southeast Texas, northeast Mexico
maculipennis var. *freeborni* (Meigen, 1818) Aitken 1939	In fresh, clear seepage water from rice fields, drainage ditches, canals and streams	Pacific slopes of United States, northwestern Mexico
pseudopunctipennis Theobald, 1901	In clear, sunny water rich in algae	Southern United States, Northern Mexico
punctipennis Say, 1823	Shaded stream beds	Southern United States
quadrimaculatus Say, 1824	In fresh water, pools, swamps, slow streams, partially shaded or entirely in the sun, with vegetation	Northeast and southeast Atlantic coast from New Hampshire, Ontario and Minnesota to Mexico
	Neotropical Region	
albimanus Wiedemann, 1821	See Neoarctic region	Mexico, Central America, northern part of South America, West Indies
albitarsis Lynch Arribalzaga, 1878	Among surface aquatic vegetation in large ponds, marshes, lagoons, flood water, inundated bayous, and large bogs with not very shady vegetation	*Central America from Guatemala to Northeastern* Argentina and Paraguay, Trinidad
aquasalis Curry, 1932 (*tarsimaculatus* in part)	In stagnant *brackish pools* from tidal swamps, sunny or shaded, less often in fresh water *rice fields* many *miles inland*	Central America (Nicaragua, Panama), Trinidad *and the lesser Antilles, southward to Brazil*
bellator Dyar and Knab, 1906	Rain water collected at the leaf base of bromeliads, shade trees	From Trinidad and Venezuela to Brazil
darlingi Root, 1926	Among surface aquatic vegetation in fresh, *clear*, shaded water of lagoons, flooded lands, *muddy* pools	Central America (British *Honduras* and *Guatemala*), South *America* (Colombia, Venezuela to Argentina)
gambiae Giles, 1902	Grassy pools, streams	Brazil
noroestensis Galvão and Lane, 1937	In fairly sunny waters as well as in shady places	*Brazil*
pseudopunctipennis Theobald, 1901	See Neoarctic region	From Mexico southward to Chile and Argentina
punctimacula Dyar and Knab, 1906	In shaded pools with stagnant water, morasses, and slow moving currents	From Mexico to Peru and *Brazil*
tarsimaculatus Goeldi, 1905	Pools	*From Colombia to Paraguay*
	Paleoarctic Region	
maculipennis atroparvus van Thiel, 1927	In brackish water of coastal areas, fresh inland water, prefers sun	From Sweden to the maritime provinces of Russia, Germany and Holland *from British Isles to Japan, from Portugal to* Italy, Mongolia

*Other valid species in the U. S. A. are:
A. *occidentalis* Dyar and Knab 1906 (*A. earlei* Vargas 1943)
A. *aztecus* Hoffmann 1935, in waters in Mexico
A. *georgianus* King 1939, deep southeast of U. S. A.
A. *bradleyi* King 1939, *along the east coast of the U. S. A.*
A. *walkeri* Theobald 1901, *a day biter in the East of the U. S. A.*
A. *crucians* Wiedemann 1828, in acid waters, southeast U. S. A.
A. *atropos* Dyar and Knab 1906, in salt waters of the Atlantic

SPECIES	BREEDING PLACES	DISTRIBUTION
	Region of Ethiopia	
funestus Giles, 1900	Grassy clear water, morasses, overgrown banks of brooks, rivers, ditches, banks of lakes, ponds, permanent seepage	Central and eastern Africa northward to Ethiopia
gambiae Giles 1902 (*costalis* Giles 1900)	Small pools of standing water, partly or wholly exposed to the sun, less frequently brackish water	Tropical Africa with the exception of desert and high mountain regions, Madagascar, Mauritius
hancocki Edwards, 1929	Clean shallow water holes with vegetation, ditches and wells, running brooks, swamps	Sierra Leone, Liberia, Cameroons, Uganda, Belgian Congo
hargreavesi Evans, 1927	In clear water, with vegetation in relatively open wooly areas in marshes, banks of streams	Sierra Leone, Liberia, southern Nigeria, Gaboon, and Belgian Congo
moucheti Evans, 1925	In vegetation on borders of marshy pools, streams, slow moving rivers, in the grass or the banks of permanent shallow morasses	Belgian Congo, Uganda, Cameroon
moucheti var *nigeriensis* Evans, 1931	Clear water with vegetation	Southern Nigeria
nili Theobald, 1904	Shaded banks of slow flowing, clear streams	Tropical Africa
pharoensis Theobald, 1901	See Paleoarctic region	Tropical Africa, Madagascar
rufipes Gough, 1910	Most frequently stagnant or semistagnant pools, sunny stream beds	Transvaal, Rhodesia, Kenya, Uganda, Sudan, North Nigeria, Gaboon

Note —Nomenclature according to American Entomological Society

GENERAL FACTS ON MOSQUITO REDUCTION

Stubbs (1945) uses the word "prevention" rather than "control" of mosquito population, as the latter word carries a connotation of willingness to accept the continued existence of the disease as being inevitable

Soper and Wilson (1942) noted that the term "mosquito eradication" has been widely misused in literature dealing with mosquito campaigns The term "mosquito reduction," not "eradication," is meant

Ginsburg (1944) has clearly stated that the primary aim of mosquito extermination work is to eliminate mosquito breeding This is generally accomplished by such mechanical methods as proper drainage, the filling in of low areas grading establishing of rapid water circulation, depending upon which method is most suitable and least costly for the topography and environment of the area to be protected Where mosquito extermination is impossible or impractical temporary control measures are resorted to The purpose of temporary control is to afford to the community immediate protection from mosquitoes It may be achieved by treating mosquito breeding places with chemicals toxic to mosquito larvae and pupae In unprotected or only partially protected areas where mosquito density has not been reduced to the minimum at which the mosquito ceases to be a discomfort to the community, various indoor and outdoor sprays and repellents against adult mosquitoes are employed

SPECIES	BREEDING PLACES	DISTRIBUTION
jeyporiensis jeyporiensis James 1902	Overflow from rice fields, irrigation channels, muddy banks of streams, lakes and ponds	Eastern India, southern China, Indochina
jeyporiensis candidiensis Koidzumi 1924	Irrigation ditches	India, China, Indochina, Burma and Formosa
leucosphyrus Dönitz, 1901	Shady pools of standing water in jungles, rocky beds of mountain springs, hoof prints	India, Ceylon, Burma, Indochina, Malaya, Sumatra, Java, Borneo and the Philippines
maculatus Theobald, 1901	Mostly in sunny stream beds, seepage, rice fields, ditches	India, Ceylon, Burma, southern China, Siam, Malaya, Indochina, Netherlands East Indies, Formosa, Philippines
minimus minimus Theobald, 1901	Slow moving currents of clear sunny water, grassy springs, irrigation ditches and rice fields	India, Ceylon, Burma, Assam, Siam, Indochina, China, Formosa
minimus flavirostris Ludlow, 1913	Frequently in clear water of shady springs around bamboo roots	Philippine Islands
novumbrosus Strickland 1916	Standing pools in woodlands, drainage ditches, swamps	Malaya
pattoni Christophers 1926	Beds of mountain streams, pockets of water in banks of streams with vegetation, *pools of rainwater in rocks*	Northern China, Japan, Korea
philippinensis Ludlow 1902	Tanks, standing pools, drainage channels, ditches, swamps, borrow pits, rice fields	Western India, Burma, Malaya, Siam, Indochina, Netherlands East Indies, Philippines
sergenti Theobald, 1907	See Palearctic region	Northwestern India
stephensi Liston 1901	See Palearctic region	India, Burma
subpictus Grassi 1899 (*rossi* Giles, 1899)	In temporary and permanent *accumulations of water, salty or contaminated by sewage*	Indies, southern China, Malaya, Netherlands East Indies
sundaicus (Rodenwaldt 1925) (*ludlowi* Theobald 1903 var. *sundaica* Rodenwaldt 1925)	Brackish pools, lagoons and *marshes formed by sea water, accumulations of salt water behind dikes and similar structures*	Eastern India, Burma, *Siam, Malaya, Sumatra, Java, Borneo, Little Sunda*
superpictus Grassi 1899	See Palearctic region	*Asia Minor to northeastern* India
umbrosus Theobald 1903	Pools of standing water and shaded woodland mires, peaty marshes in jungle	India, Malaya, French Indochina, Sumatra, Java, Borneo, the Philippines
varuna Iyengar 1924	Stagnant water in tanks, banks of springs, irrigation canals, wells	India and Burma

Australian Region

SPECIES	BREEDING PLACES	DISTRIBUTION
aconitus Dönitz 1902	See Oriental region	Celebes
hyrcanus Giles 1900	See Oriental region	Celebes
punctulatus Dönitz 1901 (probably *farauti* Laveran 1902)	Small sunny pools of rainwater, swamps, sea beds in large bodies of water	New Guinea, Timor, Melanesia, Northern Australia
punctulatus (*moluccensis* Swellengrebel and de Graaf, 1920)	Fresh or salt water, clear or polluted	Moluccas, New Guinea, New Britain, Solomon Islands, New Hebrides, Admiralty Islands, Northern Australia
subpictus Grassi 1899 (*rossi* Giles 1899)	*See Oriental region*	New Guinea
umbrosus Theobald 1903	See Oriental region	Celebes

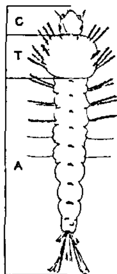


Fig 38

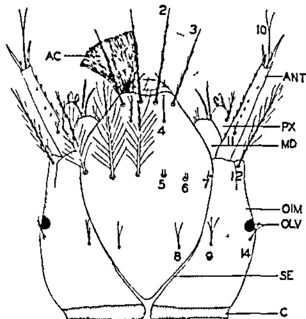


Fig 39

Fig 38 —Larva of Anopheles *C* head *T* thorax *A*, abdomen

Fig 39 —Head of larva of *Anopheles albi* . . .
dorsal head hairs *AC* cephalic fan or mouth br
OIM eye of imago *OLV* eye of larva *PX* ma
anterior clypeal hair *3* anterior outer clypeal ha
8-9, occipital hairs *10* terminal antennal hair



Fig 40

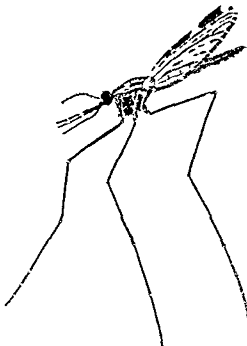


Fig 41

Fig 40 —*Anopheles quadrimaculatus* (Naval Medical School 1946) (Courtesy Cdr J W Colvin)

Fig 41 —*Anopheles albimanus* (Naval Medical School 1946) (Courtesy Cdr J W Colvin)

The first step in any malaria control program should be the assembling of facts and information bearing on the location of areas in which the disease is a problem

The more common types of surveys are blood surveys spleen surveys anopheline surveys engineering surveys and economic surveys The data obtained are plotted on maps to show foci of infection

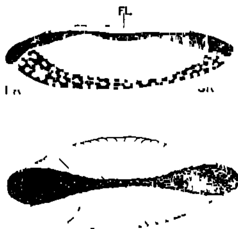


Fig 36 Egg of *Anopheles albimanus* FL floats FP frill GR exochorion.

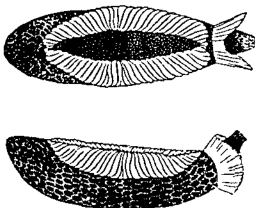


Fig 3 Egg of *Anopheles hectoris*

According to Russell (1947) valuable information concerning incidence and distribution of malaria can be obtained in a short time by examination of local children between the ages of 2 and 14 years for signs of splenic enlargement It is generally possible to attract nearly all the children of a native community to a central place by using such suitable rewards as candy beads pennies etc They will usually permit palpation for splenic enlargement and even the taking of blood smears The use of slides with a thick

light baited are useful Observations should be made of the biting habits of the different species to determine whether they bite by day or by night or whether they bite early in the evening or otherwise It is also important

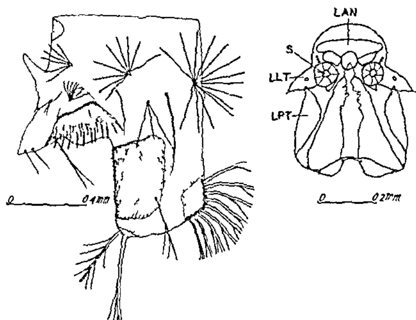


Fig 43 —Terminal segments of the abdomen and spiracular apparatus of *Anopheles fo st* *LAN* anterior plate *LLT* lateral flap *LPT* posterior plate *S* spiracle

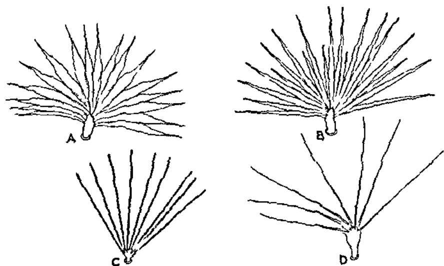


Fig 44 —Palmate hairs of subgenera of *Anopheles* *A* *Anopheles* *B* *Nyssorhynchus* *C* *Russel la* *D* *Kerteszia*

to know whether a species spends its resting hours inside habitations where it is easily attacked or whether it leaves the house at sunrise to rest outside on vegetation or in cuts depressions wells stone walls etc

smear at one end and a thin smear at the other is the best method The thin smears are examined only when confirmation of species is required

In any area under study, every type of mosquito breeding place should be sampled and the mosquito larvae identified No type of water collection from coconut shells and tin cans to wells pools ponds ditches, streams and marshes, should be neglected

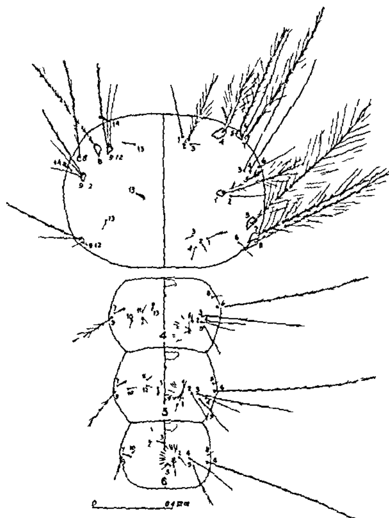
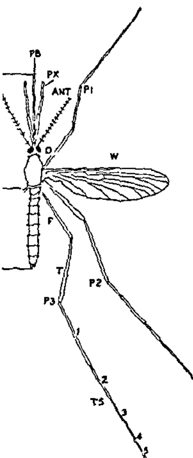


Fig 42 — Illotaxy or chaetotaxy of the thorax and abdominal segments of *Anopheles fausti* right half of diagram showing dorsal hairs left half ventral hairs

Adult mosquitoes should be collected from all types of resting places not only in habitations but also in outdoor shelters such as hollow trees underent banks and the sides of wells The collection should be made both by day and by night Hand-collecting tubes as well as traps both animal and

Mosquito breeding places vary. Those commonly encountered and readily accessible are large areas of swamps and marshes, road ditches, catch basins, ornamental ponds, water accumulations in furrows in vegetable gardens, in hoofprints of horses and cattle in pastures, etc. The kind of oil or larvicide and the type of sprayer as well as the method of application will depend upon the location and the character of the mosquito breeding place.



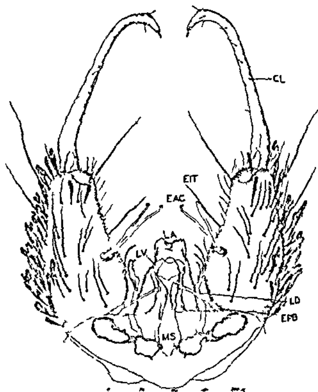


Fig 46   Fig 47

Fig 46.—Details of female Anopheles mosquito. C, head; T, thorax; A, abdomen; PB, proboscis; PX, maxillary palpus; ANT, antenna; O, eye; P1, anterior leg; P2, median leg; P3, posterior leg; F, femur; T, tibia; TS, the 5 tarsal segments; W, wing.

Fig 47.—Genitalia of male of *Anopheles albimanus*. CL, clasper; EAC, accessory spines; EIT, inner spine; EPB, parabasal spines; LA, anal lobe; LD, dorsal lobe of claspette; LV, *ventral lobe of claspette*; *MS, mesosome*.

With the advent of DDT many methods of malaria control have become unsatisfactory. They are mentioned here since in some circumstances they still may be followed, or the reader might want some general information about them.

By spraying DDT *inside* houses, our efforts are directed against adult mosquitoes, especially the females. Used in this manner, DDT will possibly

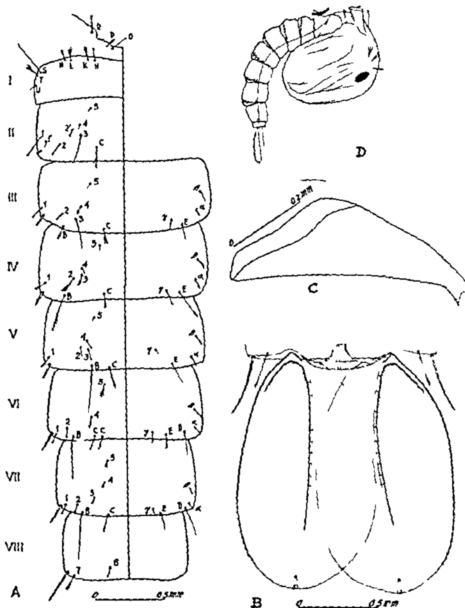


Fig. 45.—A. Chaetotaxy or chaetotaxy of pupa of *Anopheles gelajuensis*. Right half shows ventral hairs, left half dorsal hairs. *B.* Details of paddles of *A. gelajuensis*. C. Respiratory horn of the same species. *D.* Pupa of Anopheles.

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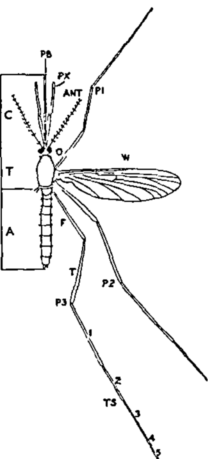


Fig 46

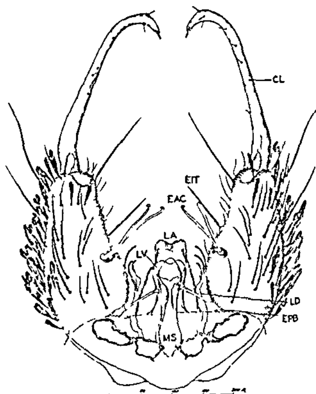


Fig 47

Fig 46—Details of female Anopheles mosquito *C* head *T* thorax *A* abdomen *PB* proboscis *PX* maxillary palpus *ANT* antenna *O* eye *P1* anterior leg *P2* median leg *P3* posterior leg *F* femur *T* tibia *TS* the 5 tarsal segments *W* wing

Fig 47—Genitalia of male of *Anopheles albimanus* *CL* clasper *EAC* accessory spines *EIT* inner spine *EPB* parabasal spines *LA* anal lobe *LD* dorsal lobe of claspette *LV* ventral lobe of claspette *MS* mesosome

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eliminate or at least significantly reduce arthropods such as bedbugs, flies, *Aedes aegypti*, and others which serve as carriers of disease—dysentery, dengue, yellow fever, etc. The purpose of spraying DDT inside houses is not to kill the very last Anopheles but rather to control the transmission of malaria.

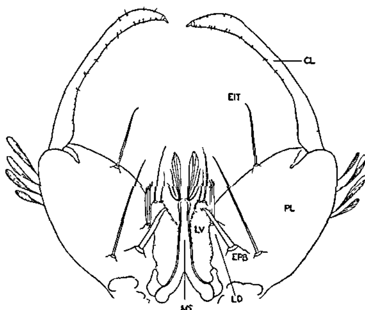


Fig. 48.—The terminalia of *Anopheles punctimacula* male. *CL*, clasper; *EIT*, inner spine; *EPB*, parabasal spines; *LD*, dorsal lobe of claspette; *LV*, ventral lobe of claspette; *MS*, mesosome; *PL*, side piece.

HOUSING

Kiker (1941) stresses the point that the only completely effective mosquito control measures are those which permanently eliminate the breeding areas, usually by drainage. The principle of this method is also applied to bodies of water which cannot be drained, such as impounded lakes. In these waters environment unfavorable to anophelines is produced temporarily at proper intervals by changing the water level. The method is combined with other measures which tend to prevent growth of marginal vegetation.

Observation of the fact that most anophelines confine their search for blood to evening and night hours when families are usually in the house has led to a search for methods of preventing entry of the mosquitoes. Mosquito proofing has been advocated by many workers. The project involves not only providing screens for doors and windows but also for closing all openings through which mosquitoes may enter a house. Where cracks in walls or floors are extensive, tar paper roofing is laid over the floor and a heavy craft paper is tacked on the walls. Plywood screens are made to fit tightly over fireplace openings (Stromquist 1944).

NETTING

Russell (1943) states that nets to protect sleeping individuals are useful in preventing malaria when they are properly employed and properly maintained. The mesh of the net should not exceed 0.050 inch (0.13 cm) to exclude all species of mosquitoes.

SCREENING

As Riley states, screening of habitations has proved to be both cheaper and more effective than mosquito bars. Today (1948) mosquito bars cost from two and one half to three dollars each. The average family requires two bars. These bed nets last only a year and serve to protect only those in bed; during the hottest weather the nets are apt to be unused because they keep out the few prevailing slight breezes.

Screens, on the other hand, protect the entire house. They cost from eight to ten dollars and last from three to five years and even longer, depending largely upon the care. They can be renewed at much less than the original outlay by rescreening the frames.

Suitable Wire and Proper Mesh

In the tropics, especially at the seaside, it is better to use wire of non-corrosive material such as bronze or aluminum. A hard drawn wire 99.8 per cent copper and of heavy gauge (0.015 inch or 0.038 cm diameter), is suitable. Aluminum screens are also good. Plastic netting promises to be a cheap and satisfactory substitute for wire. In general it is not safe to use screening with a mesh larger than 0.0475 inch (0.121 cm). Heavy grade copper wire screening has sixteen squares to the inch (about forty to the centimeter).

Installation of Screening

In installing screening care should be taken to keep breakage to a minimum. Screen doors should open outward and if possible should be on the windward side of a building. Screens should be strongly constructed so that they will not sag or warp. They require springs so that they will close automatically.

DRAINAGE

Drainage still is, and in places where practicable probably always will be, the most desirable method of effecting malaria control through local reduction or elimination of the breeding places of the malaria bearing species of mosquitoes. The rapidity with which the removal of surplus water is effected has an important bearing on malaria control. The malariologist is satisfied if removal is effected before a brood of mosquitoes can emerge.

According to Robertson et al. (1942) open earth ditches are in many instances entirely adequate and frequently the only funds that can be provided are for this cheaper initial construction. Where the finances of a community permit, lined ditches should be the choice on the basis of long life efficiency, and generally lower cost for construction and maintenance.

eliminate or at least significantly reduce arthropods such as bedbugs flies *Aedes aegypti* and others which serve as carriers of disease—dysentery dengue yellow fever etc The purpose of spraying DDT inside houses is not to kill the very last Anopheles but rather to control the transmission of malaria

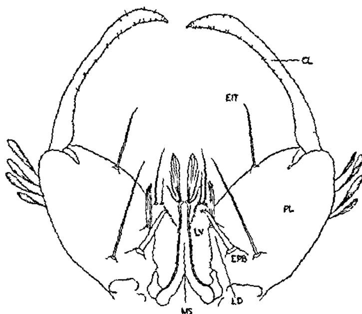


Fig 48—The terminalia of *Anopheles p nct ac la* male *Cl* lasper *FIT* inner spine *FPB* parabasal spines *LD* dorsal lobe of c asp tte *LV* ventral lobe f claspette *MS* meso some *PL* side piece

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Kerosene and gasoline may be used as larvicides since they have a marked killing effect but they form a transitory film are expensive and may constitute a fire hazard

Waste motor oils are not highly toxic to larvae They are sometimes used effectively when applied in a fairly thick film Better results are obtained when waste motor oil is mixed with kerosene in the proportion of 1 to 3 with addition (if possible) of about 2 per cent of castor oil The amount of kerosene to be added will have to be determined by experiment

The amount of oil needed to produce a uniform killing film under field conditions usually ranges from 25 to 60 gallons per acre depending upon the nature of the breeding area toxic properties of the oil species of mosquitoes method of application and atmospheric factors such as wind temperature etc

Handling of oil is objectionable from the standpoint of fire hazards especially near shipyards lumber yards ammunition factories and storage places open fire barrels etc

Oil soaked dust may be scattered over the surface of a breeding place Russell (1943) makes the point that oil booms may be used to combat larval drift The larvae are killed by oil soaked sawdust or chaff thrown on the surface of the water above the boom Russell (1943) states that when Diesel oil No 2 is used about 9 gallons (34 liters) are required per acre (about 4 000 square meters) of water surface for complete coverage with a uniform stable film With an ordinary knapsack sprayer of the Panama type one laborer can oil about 5 acres (about 20 000 square meters) of breeding area per day if the terrain is not difficult In general practice the amount of oil necessary to produce a uniform film may vary from 10 to 20 gallons (38 to 76 liters) per acre The amount of floatage and vegetation makes a considerable difference

Usually it is necessary to spread oil once a week

Fuel oil will kill the larvae in less than one hour The amount of oil required ranges from 10 to 30 gallons per acre of water surface depending upon the amount of vegetation or debris present

Where oil is dispersed by currents as in streams and ditches it may be better to attempt constant application For this purpose there are at least three types of continuous oilers none of which is entirely satisfactory A continuous oiler requires a good deal of attention generally uses more oil than would be dispensed over the same areas from a knapsack sprayer and should not be used unless other methods are found impractical

PYRETHRUM

According to Sinton and Wats (1935) the use of pyrethrum flowers for insecticidal purposes appears to have originated in Persia It was introduced into Europe early in the nineteenth century At that time and for many years afterward a powder prepared from the flowers has been used for domestic purposes

WATER FLUCTUATION

Experiments with intermittent irrigation or a so called ' turn system'' to control mosquito breeding in rice fields have brought promising results in India Java Portugal and other places The principle of this method as a malaria control measure involves the periodic withholding of water long enough to permit the surface of fields and channels to become sufficiently dry to cause the death of mosquito larvae The subsurface soil around the rice roots remains moist

Anopheline vectors that breed in streams may be controlled by periodic sluicing A small dam is built to impound water which can be released by manual or mechanical removal of a barrier or by use of automatic siphons

OIL

The use of oil for mosquito reduction was recommended as early as 1793 in an article in *The American Advertiser* of Philadelphia on August 29 A similar suggestion attributed to R Southey was made in the book *Omniana Otiosores* published in London in 1812 But it was not until Howard published his work in 1892 that the application of oil to mosquito control became an established practice

Herms and Gray (1940) give it as their opinion that the correct use of oil or larvicide is to supplement other measures that are in use to eliminate mosquito breeding places They also point out four other circumstances that call for use of oil (1) while pending installation of primary measures (2) as an emergency measure following floods or other unusual conditions (3) as the only available method in a few instances where primary measures such as drainage are not applicable (*i e* impounding reservoirs) and (4) in the relatively few cases where the capitalized annual cost of oiling or larviciding is considerably less than the cost of primary control measures

The following properties are desirable in the ideal mosquito oil quick toxic effect upon larvae and pupae good spread on all kinds of waters rapid penetration through debris and thick vegetation a stable long lasting film odor inoffensive to man absence of injurious effects on fish waterfowl and plant life and low cost (Ginsburg 1944)

The ideal specifications for a larvicidal oil are

Specific gravity 20/4	0 83 0 86
Viscosity (Saybolt Universal at 100° F)	31 43
Initial boiling point	297 414° F (165 230° C)
Final boiling point maximum	800° F (426 7° C)
Spreading coefficient minimum	17 0

The most important disadvantages of the oiling process are (1) the difficulty of reaching the water through a matt of vegetation and (2) the diminution of the effect by the action of wind and rain The chief advantages are the destruction of eggs larvae and pupae of all kinds of mosquitoes ease of obtaining and spraying ease with which results can be observed and of course the factor of nontoxicity

is based upon actual performance in tests These sprays should contain 150 *to 180 Gm of pyrethrin or their equivalent in each 100 c c With either of the* two kinds of sprays about one half ounce (15 c c) is required to spray 1 000 cubic feet (about 28 cubic meters) (3) The third type of product used *by the* Army is pyrethrum in containers holding a mixture of 20 1 concentrate sesame oil and liquid Freon—Freon 12 The preparation can be of 18 ounces *(532 c c) of a mixture of liquid Freon Freon 12* or dichlorodifluoromethylene with 0 8 per cent wax free pyrethrin and 6 0 per cent sesame oil The latter enhances the killing power of the pyrethrin The vapor pressure of the solvent produces the necessary spraying pressure which does not decrease as long as liquid is present in the closed container As the Freon 12 containing the in secticide is sprayed it forms a fine mist from which the solvent evaporates almost immediately leaving the pyrethrum and sesame oil suspended in the atmosphere as a cloud of fine droplets called an aerosol Freon 12 is nontoxic to man and is noninflammable Its role in the spray is simply that of expellent *to disperse the pyrethrum sesame oil*

Popularly known as a " health bomb " each dispenser of this kind is said to carry enough insecticide to fumigate 240 pup tents or a giant bomber or a space of 150 000 cubic feet

Pyrethrum insecticide can be effectively sprayed through any ordinary spray gun used for spraying paint if air pressure of 15 pounds (7 kilograms) or more is supplied Pressure may be supplied from a tank pumped up by hand or from gasoline or electrically driven compressors Solidified carbon dioxide Dry Ice when available in suitably constructed pressure tanks is a good expedient

PARIS GREEN

After the work of Roubaud in 1920 on the larvicidal properties of para formaldehyde trioxymethylene Barber and Hayne (1921) discovered the prop erties of Paris green as an effective larvicide This product has several names among them Schweinfurth green Imperial green Emerald green and *Mitis green*

Bishop (1940) reported no deleterious effect of Paris green upon vegeta tion and gave no evidence of destruction of aquatic organisms that are im portant as fish food

Sweet and Rao (1933) reported complaints of skin eruptions suffered by *laborers engaged in mixing and spreading the Paris green* larvicide The erup tions occurred principally in the axillary inguinal and anal regions They were not serious and disappeared after the workmen had been instructed to bathe and to wash their clothes thoroughly immediately after work

Larvae feeding at the surface ingest Paris green particles This is espe cially true of *Anopheles* larvae *however* when Paris green floats long enough in still water it is ingested by Aedes and by some Culex larvae which feed part time at the surface

Paris green after sinking is usually rendered inert *It does not repel* ovipositing mosquitoes

Steudel (1911) called attention to the possible value of the insecticidal sprays in malaria control Giemsa (1911 1912 1913 1914) finally recommended a mixture consisting of tincture of pyrethrum soft soap and glycerine diluted with water he also reported that the use of a soap solution containing formaldehyde was effective and cheap

In the United States kerosene extracts of pyrethrum flowers began to displace the powder for household use (about 1900) As a result a large number of proprietary insecticidal sprays are now on the market The active principle in these is derived for the most part from pyrethrum

The name pyrethrum applies to the dried flower heads of *Pyrethrum cinerariaefolium*

Pyrethrin I and Pyrethrin II were isolated from pyrethrum by Staudinger and Ruzicka (1924) They are viscous liquids soluble in petroleum ether alcohol acetone ethylene dichloride and in most of the other organic solvents

These two substances are toxic to cold blooded animals such as insects fish frogs crabs and turtles *The pyrethrins are harmless to warm blooded animals* when taken by mouth

Ginsburg (1930 1939) has developed the New Jersey pyrethrum larvicide It is essentially an oil emulsion of approximately the following composition 66 per cent kerosene or similar light petroleum distillate 0 07 per cent pyrethrin (equivalent to extract of one pound of flowers analyzing at 0 9 per cent pyrethrin per gallon of gasoline) 33 5 per cent water and 0 5 per cent of a neutral emulsifier such as commercial sodium lauryl sulfate This concentrated stock emulsion is mixed with about ten parts of water before spraying Although the diluted spray contains only about 6 per cent kerosene the small quantity of pyrethrin greatly increases its toxic properties so that when applied as directed it is equally as efficient as the regular mosquito oil in destroying larvae and pupae

Russell (1943) considers the spray killing of adult mosquitoes with pyrethrum extract as one of the most important measures of malaria control When used against malaria vectors which rest indoors during the day this solution will destroy a high percentage of the infective mosquitoes of an area and will destroy also many potential vectors The spray also acts as a repellent keeping mosquitoes away from sprayed dwellings and from circumscribed outdoor areas which have been sprayed

The United States Army used three types of pyrethrum products (1) 1 20 concentrate each gallon (3 8 liters) containing the oleoresins of approximately 20 pounds (9 kilograms) of flowers with no less than 75 to 100 Gm of total pyrethrin per gallon (2 to 2 5 Gm per 100 c c) This concentrate in Army practice is diluted with 14 parts of good quality water white gasoline and may be used in various types of mechanical sprayers such as those described below (2) A prepared ready to use pyrethrum spray is supplied in areas where there may be difficulty in obtaining kerosene for diluting the concentrate This spray conforms to class AA rating as defined by the United States Department of Commerce (1938) standard specifications The rating

DDT or any other insecticide is not a substitute *for good sanitation such* as the permanent removal of insect breeding areas

It has been demonstrated that malaria can be effectively and cheaply reduced *in towns and villages* by spraying the interior of houses

DDT with Thanite (*terpene thiocyanoester*) *gives a strong knockdown* and high kill "

Experiments made in Arkansas during the summer of 1944 show that a *single application of DDT* greatly reduces the number *of mosquitoes* resting in buildings during the day *for a period of about 130 days The experiment* also indicated that enough adults were killed to lower the larval population breeding in rice fields by more than 50 per cent

Since *DDT* attacks both adult and larval stages of the mosquito spraying results in immediate kill *as well as affecting future breeding DDT is water* insoluble and must be sprayed either in powder form or in solution in organic solvents such as kerosene xylene o dichlorobenzene etc or in water emulsion *Two quarts of 5* per cent solution per acre *have* given complete protection for several weeks

Solutions of 2 5 per cent DDT in kerosene gave effective control of anopheline larvae when applied by boat oiling units at a rate of approximately *0 1 pound of DDT per acre making possible* a reduction *of about 98 per cent in* the amount of kerosene normally used

DDT had to be mixed with 95 per cent soapstone before a satisfactory airplane dusting combination was obtained With this mixture 90 per cent *control of A quadrimaculatus larvae was effected over 200 foot swaths at rates* as low as 0 05 pound per acre Certain polymethylnaphthalenes (Velsicol) having a high solubility and a high boiling point were found to be ideal solvents for making liquid solutions of DDT to be applied by airplane One *objection to airplane sprays in this instance is their invisibility* The high visibility o [illegible] ing swath

DDT dusts applied at rates of 0 1 pound per acre gave [illegible] f *injury to aquatic organisms* other than mosquitoes but 5 per cent solutions of DDT in kerosene applied at rates of 0 1 to 0 25 pound per acre were quite destructive to populations of aquatic insects living in close contact with the water surface especially *Hemiptera and Coleoptera* Water boatmen (Corixidae) were especially susceptible to the DDT spray Actual dipping records showed however that 20 per cent solutions of DDT in Velsicol applied as thermal aerosols at rates of about 0 12 pounds *DDT* per acre gave very efficient *anopheline control* without significant reduction of other aquatic organisms such as May fly larvae midge larvae beetle larvae and water fleas (Cladocera)

DDT is highly poisonous *to water fleas and fish and to some of the other cold blooded animals* It has killed birds that had fed upon insects killed by the chemical It is deadly to honey bees DDT may interfere with adequate pollination of important food and seed crops and it does destroy *beneficial insects that keep certain injurious pests under control* It is not harmful to

In Paris green mixtures the vehicle may be powdered charcoal calcium hydroxide powdered soapstone road dust or some other dust The vehicle must be well mixed with the poison When lime is used Paris green may be added in the proportion of 10 per cent by weight This is equivalent to about 5 per cent by volume

A Paris green dust mixture can be applied to ponds lakes and large streams by being blown into the air from the windward side so that it will form a cloud and be carried out over the water The large hand operated or motor operated dust blower ordinarily employed in dusting trees in horticultural work may be used to throw the mixture into the air For large bodies of water a slowly settling dust carried along by a light wind will give best results For small bodies of water where vegetation is heavy, or for ditches and streams that are too narrow to be dusted by the cloud' method handfuls of the dust mixture may be thrown directly on or into the vegetation and on the surface of the water There are automatic distributing devices for small canals and streams The airplane may be used to apply the dust over large areas, e g extensive swamps In general the best results are obtained on a sunny day after the dew has evaporated from the vegetation When special distributors are not available Paris green mixed with wet or dry sand clay or any other kind of earth or small pebbles and thrown by hand is often effective

The amount of larvicide required to treat an area will vary with the amount of vegetation When the surface of the water is clear about one half ounce (14 Gm) of Paris green mixed with 99 parts of dust by volume is sufficient to dust 1 000 square feet (93 square meters) of water surface Where the vegetation consists of grass or reeds greater quantities must be used In such places the percentage of Paris green should be from 2 to 5 per cent by volume as determined by experiment

One man can usually prepare and spread Paris green mixture along 1¼ miles (2 kilometers) of bank in one day the exact distance depending upon local conditions

Under average conditions Paris green should be applied at intervals of from five to seven days in warm weather Dusting should be repeated without delay whenever examination of the water reveals the presence of fourth stage larvae Dusting otherwise needs to be applied only often enough to prevent development of first stage larvae and of new broods

According to Watson and Kiker (1938) the cost of operating a dusting plane varies considerably but may be set at about forty dollars per hour An airplane flying at the rate of eighty two miles per hour can dust 33 acres per minute at the cost of 36 7 cents per acre

DDT

DDT acts as a poison for the stomach of the larvae and as a contact poison for the adults Its most remarkable characteristic is its prolonged toxic action the residual effect

Although mosquito repellents contribute toward relief from annoyance, their application on the skin entails inconvenience. *They repel mosquitoes only by actual contact.* To be effective they must completely cover all exposed parts of the body. They cause smarting of delicate parts of the skin, such as eyelids and face. The irritation may become well nigh unbearable to highly sensitive individuals in a warm humid climate when they perspire freely (Ginsburg, 1944).

RELIEF FROM MOSQUITO BITES

Irritation resulting from mosquito bite may be relieved by moist soap. Howard and Bishop (1932) advise wetting the end of a cloth with lather from ordinary toilet soap and rubbing gently on the puncture.

Hoffman (1941) recommends the local application of chloroform.

CHEMICAL PROPHYLAXIS

Russell (1943) emphasizes the necessity of proper treatment of all malarial cases in the work of control of malaria. Drug prophylaxis or chemoprophylaxis has a long history. It was tried against malaria long before the cause of the disease was known. Quinine and Atabrine in small doses are almost equally useful in suppressing the appearance of clinical symptoms after infection. The usual clinical chills and pyrexia are suppressed and do not reappear *until* prophylactic medication has been stopped. Some authorities believe that it is safe to delay the suppressive treatment for three or four days after such treatment has been indicated. There are data, however, which indicate that at least 0.6 Gm. of Atabrine should be taken within a period of two weeks to produce levels in the blood plasma at which suppressive effects are seen.

WILD LIFE

Actual work and study have led to the conclusion that in spite of controversies which may exist between wildlife conservationists and those interested in malaria control, the program of malaria control does not have any serious effect upon wildlife.

PLANTS

Aquatic plants play a dominant role in malaria control inasmuch as they provide food and shelter for the larvae of the vector (Penfound, 1942). Several studies have been made, especially on herbicides, to determine the relation of each species of plant to anopheline propagation and to devise methods of reducing objectionable species to an innocuous state.

Chara foetida has been reported as having a marked lethal effect on mosquito larvae. Shading has been used with some success in control of Anopheles. The factors involved in shading are, on the one hand, the reduction of illumination and, on the other, the retention of moisture by the roots of the plant. Shade may prevent algae and other vegetation from flourishing.

Some success has been obtained in afforesting with *Eucalyptus robusta* to dry the Uganda swamps where *A. gambiae* and *A. funestus* breed.

most plants but does damage squash and other members of the squash family When applied at the rate of 25 pounds per acre, it was found that it could retard growth of some plants The human skin is not harmed by the dry substance or by the water suspensions, and one scientific worker took as much as 1 5 Gm of DDT in butter without ill effects

Massive doses, such as a teaspoonful taken by mouth, or constant and excessive exposure of the skin to DDT oil solution may cause toxic reactions DDT should always be properly labeled It should not be stored near food nor sprayed on food or food utensils

Persons engaged in spraying with DDT should wear coveralls, a wide brimmed hat, goggles, a chemical cartridge respirator, and rubber gloves Persons applying such sprays infrequently need to wear merely coveralls that may be changed after spraying and should avoid wetting the face or any part of the body by the spray When the spraying is done inside the home, all open fires should be extinguished Babies' beds, children's toys, food, or utensils for eating or drinking should not be sprayed Since DDT spray stains glass, pictures and mirrors should be removed from the walls Any liquid spilled should be wiped up Pets should be excluded from the house until the spray dries When DDT dust is applied in a confined area, a dust respirator should be used (Van Keek, 1945)

If skin or eye inflammation occurs from DDT spray, the affected parts may be treated with warm boric acid solution every few hours, if necessary, until a physician is consulted If DDT is swallowed mustard water (one tablespoon of mustard to a glass of warm water) should be taken immediately to induce vomiting Medical help should be enlisted Twenty c c of 10 per cent calcium gluconate has been found useful in DDT poisoning (Vaz et al 1945)

PHENOTHIAZINE

When Paris green and other larvicides are not available phenothiazine mixed with dust or used in water is an effective substitute It is less stable than Paris green but floats better

COPPER SULFATE

Copper sulfate has been used, at final dilutions of 0 1 to 0 25 ppm of water, to kill algae Some species are resistant to this concentration Its use is not generally accepted because of the odor of the dead algae and because of the objectionable taste imparted to the drinking water

REPELLENTS

Various chemicals possessing repelling properties have been recommended and commercialized These chemicals are applied to the skin in the form of lotions, ointments, or powders They may protect the individual for a period of up to several hours, depending upon the repellent properties and other factors, such as thoroughness of application, species and density of mosquitoes, atmospheric factors, etc (see Chapter 65)

Although mosquito repellents contribute toward relief from annoyance their application on the skin entails inconvenience They repel mosquitoes only by actual contact To be effective they must completely cover all exposed parts of the body They cause smarting of delicate parts of the skin such as eyelids and face The irritation may become well nigh unbearable to highly sensitive individuals in a warm humid climate when they perspire freely (Ginsburg 1944)

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FISH

In wells, gardens, and pools without much vegetation, some help in larva control may be gained by use of larva eating fishes, such as *Gambusia affinis*

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unite with the anterior third A flagellum which stems from the blepharoplast is directed forward, following the outline of the parasite, with a few undulations, and extending beyond the anterior end as a free flagellum It is about one half or three fourths the length of the trypanosome The narrow space between the flagellum and the side of the body is occupied by the undulating membrane, which has a few folds

Fig 49 shows a specimen, enlarged 2,000 times, of *T cruzi* in human blood, stained with Giemsa stain It shows the details which permit identification of the species in blood slides

In contrast to other known pathogenic trypanosomes, *T cruzi* does not multiply in the blood This process takes place within the tissues of practically all organs, especially in the cells of the reticuloendothelial system Here, after the trypanosome becomes immobilized, it loses its flagellum and undulating membrane and is reduced to a protoplasmic mass, 3 to 5 microns in diameter, with two nuclei One nucleus, bar shaped, is the kinetonucleus or blepharoplast, the other, more or less circular, properly called "nucleus," through successive binary fission gives rise to clusters, misnamed cysts or residual forms, of leishmanias of *T cruzi*

In Fig 50, in a large endothelial cell of a lymphatic gland, a group of leishmanial elements is seen, with a frequent tendency to produce elongated, flagellated forms Fig 51 shows the same forms in the heart, where they are found more often



Fig 49 —*Trypanosoma cruzi* in human blood Giemsa stain (X2000)

By reacquisition of the flagellum, derived from the blepharoplast, and by progressive enlargement of the leishmania form of the parasite, there occurs transformation into flagellar elements, called *crithidia*, in which state they are capable of multiplication Then, by displacement of the kinetonucleus of the crithidia from the anteronuclear position, which characterizes them, to the posterior extremity, becoming terminal, the crithidia are converted into *trypanosomes* which invade the circulation and begin again the parasitic blood to tissue to blood cycle, with a dual personality, so to speak One form is the trypanosome form, motile and nonreproducible in the blood of mammals but circulating in it *(hemoparasitic)*, the other form is the leishmania form, nonmotile, and not multiplying, evolutive, and adaptable to the tissues *(histoparasitic)* (see Fig 52)

Trypanosomes are ingested by triatomas along with the blood of mammals They undergo special transformation in the digestive tract, particularly in the mid gut of the bug The blepharoplast approaches the nucleus, the undulating membrane is lost, the parasite becomes rounded From these elements originate the crithidial forms, with anteronuclear kinetonucleus Their motility, until the kinetonucleus shifts into the postnuclear but not yet terminal position results in the formation of trypanosomes called "metacyclic" (Brumpt) These are infectious and accumulate in the lower intestine or rectum of the bug and are eliminated with the excreta

Mucosae in general, also the conjunctiva, constitute portals of entry for "metacyclic" trypanosomes from the dejecta of the triatoma Penetration may occur even through the

CHAPTER 8

CHAGAS' DISEASE

SALVADOR MAZZA†

DEFINITION

Chagas' disease is an infectious, noncontagious disease caused by Trypanosoma cruzi (Chagas, 1909) Erroneously believing that during a certain stage in its life cycle in man *Trypanosoma cruzi* multiplied by schizogony, Chagas renamed it *Schizotrypanum cruzi* However being based on mistaken conception, this name was withdrawn by E Chagas in 1934 and the original name given it by C Chagas, *Trypanosoma cruzi*, is now the accepted name of this species

The disease affects several species of animals and attacks at all ages (neither excluding nor preferring children) insofar as man or animals are exposed to contamination by the transmitting bug, a triatoma

This bug inhabits huts and other primitive dwellings or old adobe houses in ancient towns It is a strict hematophagous Hemiptera It is known as "vinchuca" in Spanish American countries, as 'barbeiro" in Brazil and as the "kissing bug" in the United States, because it so often stings the face this frequently being the only exposed part of the sleeping individual (See Chapter 55)

Chagas' disease is also called "American trypanosomiasis" or "schizotrypanosis" It derives its name from Carlos Chagas, who first discovered the vector agent Later, in 1907 he discovered the causative agent, *T cruzi* He described the disease itself in 1909 the natural domestic carriers of the trypanosome (cats, 1909) wild animal sources (armadillos 1912), and, finally the clinical manifestations in detail (1916)

The term "parasitic thyroiditis" heretofore used to designate Chagas' disease, should disappear since there is no justification for its use

THE CAUSATIVE AGENT TRYPANOSOMA CRUZI

(Chagas, 1909)

This trypanosome, in the blood of man, is characterized by the terminal or juxtaterminal position of the blepharoplast or kinetonucleus in the posterior extremity of the body The kinetonucleus, because of its size, extends beyond the sides of the parasite at the posterior end, giving the appearance of an apple with a dagger thrust through it The nucleus, usually ellipsoid or ovoid and compact, is located at a point where the last two thirds of the organism

…ie Regional Mission Pathologic
All illustrations are originals
Jörg Dr Germinal Basso Dr
S Miyara and Dr J Lovaglio
…ingleness of purpose overcome

†Dr Mazza died on July 13 1946

unite with the anterior third A flagellum which stems from the *blepharoplast* is *directed* forward following the outline of the parasite, with a few undulations, and extending beyond the anterior end as a free flagellum It is about one half or three fourths the length of the trypanosome The narrow *space between the flagellum and the side of the body* is occupied by the undulating membrane, which has a few folds

Fig 49 shows a specimen, enlarged 2,000 times, of *T cruzi* in human blood, stained with *Giemsa stain It shows the details* which permit identification of the species in blood *slides*

In *contrast to other known* pathogenic trypanosomes, *T cruzi* does not multiply in the blood This process takes place within the tissues of practically all organs, *especially in the* cells of the reticuloendothelial system Here, after the trypanosome becomes *immobilized*, it loses its flagellum and undulating membrane and is reduced to a protoplasmic mass, 3 to 5 microns in diameter, with two nuclei One nucleus, bar shaped, is the kinetonucleus or blepharoplast, the other more or less circular, properly called "nucleus," through successive binary fission gives rise to clusters, misnamed cysts or residual forms, of leishmanias of *T cruzi*

In Fig 50, in a large endothelial cell of a lymphatic gland, a group of leishmanial elements is *seen*, with a frequent tendency to produce elongated, flagellated forms Fig 51 *shows* the *same forms in the heart*, where they are found more often



Fig 49 —*Trypanosoma cruzi* in human blood Giemsa stain (×2000)

By *regeneration* of the flagellum derived from the blepharoplast, and by *progressive en*

dual personality, so to speak *One form* is the trypanosome form, motile ...
in the blood of mammals but *circulating in it (hemoparasitic)*, the other *form* is the leishmania form, nonmotile, and not multiplying, evolutive, and adaptable to the tissues *(histoparasitic)* (see Fig 52)

Trypanosomes are ingested by triatomas *along* with the blood of mammals They undergo special transformation in the digestive tract, particularly in the mid gut of the bug The blepharoplast approaches the nucleus, *the undulating membrane is lost, the parasite* becomes rounded From these elements originate the *crithidial forms*, with anteronuclear kinetonucleus. Their motility, until the kinetonucleus *shifts into the postnuclear but not yet terminal* position, results in the formation of trypanosomes called "metacyclic" (Brumpt) These are infectious and accumulate in the lower *intestine* or rectum of the bug and are eliminated *with the* excreta

Mucosae in general, also the conjunctiva, *constitute* portals *of entry* for "metacyclic" trypanosomes from the dejecta of the triatoma Penetration *may occur* even through the



Fig 50.—Histiocyte of a lymphatic gland with leishmanial elements of *Trypanosoma cruzi* (evolutionary dual form of the parasite)



Fig 51.—Group of leishmanial elements of *Trypanosoma cruzi* in the human heart.

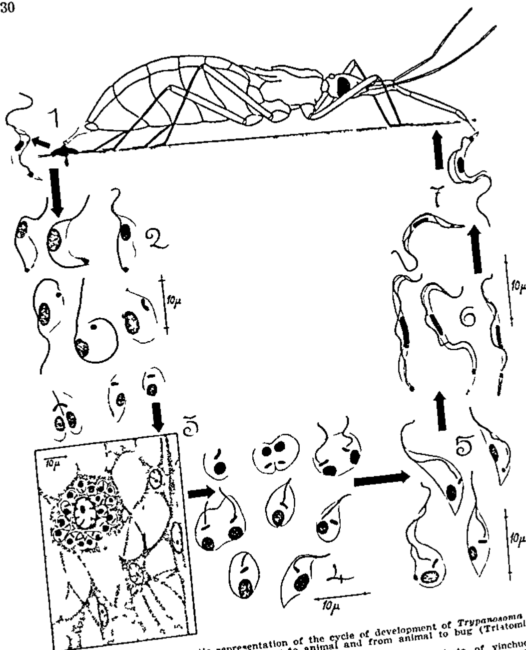


Fig 52—Diagrammatic representation of the cycle of development of *Trypanosoma cr* in animal and human infection from bug to animal and from animal to bug (Triatomina (After M E P R A) (Original of Dr M L Jörg)

1 Penetration into animal by metacyclic trypanosomes from dejecta of vinchuca Initial forms of development—dejecta of vinchuca injected intraperitoneally into newborn c smear of exudate after 6 and 12 hours Note the ameboid rounding off and loss of flagell with transformation into leishmanioid elements 3 Leishmania forms in hypertrophic leucocy some showing enlargement of blepharoplastic pole Histologic section of lymphatic gland dog peritoneally injected 4 Developmental forms in parasitic foci of tissue Smear of car muscle (white rat) forty fourth day of experimental infection Crithidia forms derived f leishmania forms 5 Crithidia forms and leptomonas forms precirculatory Smear of phragmatic gland (newborn dog) dog inoculated peritoneally with dejecta of vinchuca for day of infection 6 Metacyclic precirculatory trypanosomes (exceptional in blood) c material as 5 7 Infestation of vinchuca by trypanosomes sucked up in the circulating b of the cutaneous capillaries

Fig 50 —H stiocyte of a lymplatic gland with leishmanial elements of *Trypanason a cru* (e olutionary dual form of the paras te)

g 51 —Group of e shmanial e en ents of *Trypanoson a cru* i in the human heart

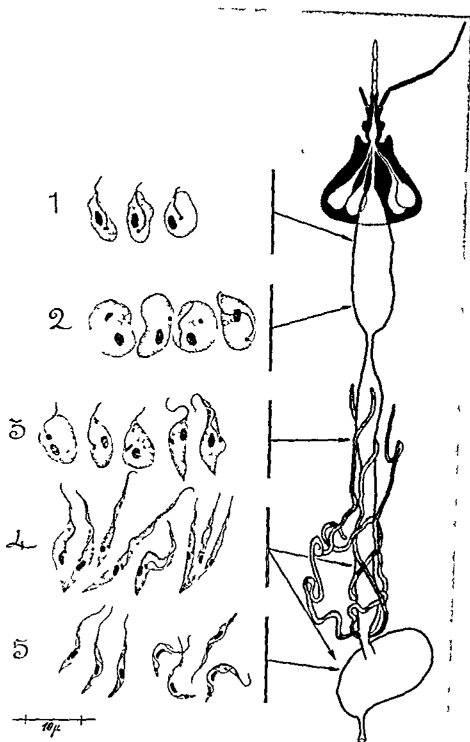


Fig 54.—(Legend on opposite page.)

intact skin, especially in the newborn and in infants In contrast to infection with *Trypanosoma gambiense*, the cause of African sleeping sickness, which enters the human organism by *inoculation* of the trypanosome from the salivary glands of the tsetse fly, the vector, Chagas' disease is a result of *contamination* by excreta of the intermediary vector upon the mucous membranes, on the mucosa of the digestive system, or into the skin, through lesions produced by scratching

The bite of the bug may also cause infection in the presence of moisture which aids the penetration of the trypanosomes from the dejecta deposited frequently by the triatoma while engorging blood or through regurgitation of the trypanosomes from the mid gut to the pharynx and proboscis

Moreover, infection may occur without intervention by the vector It may take place through the placenta, or it may occur through the milk of the mother or the wet nurse if they harbor parasites in their blood, by transfusion of blood containing trypanosomes, by abrasions of the skin of the hands when skinning wild animals which are natural carriers of *T cruzi* (cooks, taxidermists, armadillo hunters, etc), through accidentally spurting blood into the eyes, through contact with the conjunctiva by infected fingers in laboratory personnel

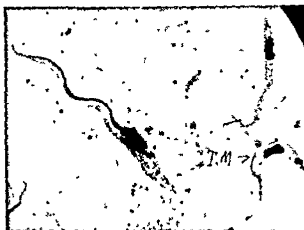


Fig 53 —Dejecta of triatoma with crithidias and a metacyclic trypanosome (*TM*) *Trypanosoma cruzi*

By using the excreta of infested transmitting bugs or the blood of mammals infected with *T cruzi* the parasites may be grown in artificial culture media containing rabbit blood, especially that of Novy Neal and Nicolle (NNN agar) Kelser, or German In these nutrient media after five days, flagellates of crithidia and also the *leptomonas* type may be seen in the water of condensation The latter is differentiated from the former by lack of the undulating membrane

When the culture is inoculated into mammals, trypanosomes appear in the blood, and production of clusters of leishmanial forms takes place in the tissues, especially in smooth and striated muscle, just as when infected blood or infected triatomas are injected

VECTORS

(See Chapter 55)

Natural Reservoirs of Trypanosoma Cruzi

Aside from dogs and cats, quite frequently the carriers of *T cruzi* in homes infected with the trypanosome, there are numerous species of animals with natural infection

The most common of these which have been proved in Argentina are as follows

Edentatae

Chaetophractus vellerosus vellerosus (quirquincho)

Chaetophractus villosus (peludo)

Zaedyus pichyeaurinus (piche)

Dasypus novemcinctus (tatu or mulita [nine band armadillo] of Paraguay)

Tolypeutes matacos (quirquincho bola or mataco)

Marsupialia

Didelphis paraguayensis (comadreja overa) (brown weasel)

Lutreolina crassicaudata paranalis (comadreja colorada) (red weasel)

Canidae

Pseudalopex culpaeus culpaeus (red fox)

Mustelidae

Grisonella huronax (huron

PATHOGENESIS AND PATHOLOGIC ANATOMY

Chagas disease is a protozoan affection of purely an inflammatory type and is not a disease entity of the reticuloendothelial system The predominance of parasites within the cells of the reticuloendothelial system is due to their physical nature since leishmanial and evolutionary forms of *T cruzi* are large corpuscles which strongly stimulate macrophagy of the reticuloendothelium But this macrophagy always occurs toward the end of the inflammatory stage and not in the primary period

The acute primary phase of Chagas' disease is transitory It can be recognized by biopsy of the primary lesion (chagomas) in the skin or of neighboring adenopathy There are foci of acute inflammation at the point of entry of the parasite the infiltrations resembling furuncles or pyogenic phlegmon in its first stages

At the point of the first ectodermic inflammatory focus (the portal of entry of the parasite) there occurs a lymphatic and hematogenous dissemination of the parasite The presence of *T cruzi* in the blood is only an *epiphenomenon* of Chagas disease since fundamentally this is a visceral disease and the most important changes in the development of the protozoa occur in the tissues

During the development of the primary ectodermic infection *the chagoma of inoculation* a typical acute inflammation there occur two essential phases in this infectious focus

1 Multiplication of the parasite, since the invaded animal body does not overcome the infection

2 Lysis or disintegration of some of the parasites which succumb to the infection reabsorption of substances derived from living parasites and flooding of the body by parasites carried in the blood stream Cytologically the reactions of the body to the parasitic invasion are characterized by histiocytic hyperplasia with or without the presence of parasites in lymph glands liver and spleen

The active multiplication of the parasites in the primary focus of infection is followed by early liberation into the blood stream It may occur at



Fig 55

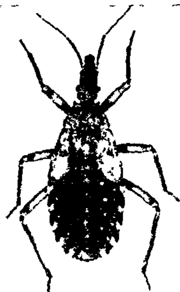


Fig 56

Fig 55 —Imago of *Triatoma infestans* (approximately ×4)

Fig 56 —Apterous nymph (alares outlined) of *Triatoma infestans* (approximately ×7 or 8)

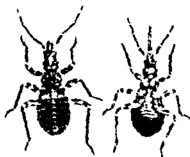


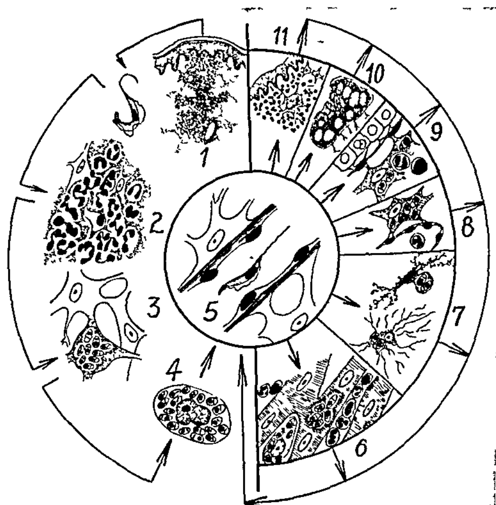
Fig 57 —Larvae of *Triatoma infestans*, recently emerged (approximately ×12) At right, ventral view with rostrum extended in position adopted by bug when ready to bite

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Fig 54 —Evolution of *Trypanosoma cruzi* in the digestive tube of *Triatoma infestans* (After M E P R A) (Original of Dr M F Jörg)

At first, Chagas described a period which he called *acute* He extended this period to include the stage of disappearance from the blood of all directly demonstrable trypanosomes After this phase, according to Chagas, there followed another period, the *chronic period,* which lasts throughout the patient's life

Chagas demonstrated *T cruzi* in the blood by direct examination of fresh blood and believed that the acute stage of the disease existed for about one



(After Mazza and Jörg)
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leishmanias in reticular
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periodically) *6* and *11*
T cruzi with the final

the site of the chagoma or of the neighboring adenopathy Finally, the primary inflammatory focus loses its reactive intensity and there follows a regressive phase of reabsorption and cicatrization and by hematogenous dissemination the attack of the trypanosomes against the tissues begins

The parasites freed from their primary fixation migrate by means of the blood stream into the tissues Here they attack in the manner of parasites in the primary infection The tissue responds with an inflammatory reaction similar to the former However the exudative phase each time becomes shorter because of the formation by the body of macrophages which serve to anchor and isolate the parasite especially when it is large

It may then be said for Chagas disease in man that finding extensive histiocytic macrophagy of parasites with such overwhelming evidence as gigantic cysts or multinucleated plasmodia is simply the end of the focal inflammation as a result of *endogenous reinfection* by *T cruzi* It is the stage preceding that of the cicatrix

T cruzi has the property of rapidly adopting the fertile leishmania form in fixed tissues This parasitic form is probably more resistant than is the evolutionary flagellate form and may also present less antigenic capacity than the other

It is for this reason that with a combination of (1) histiocytic hyperplasia (2) allergy and (3) less antigenic capacity of the leishmania forms there follows *inflammation of endogenous reinfection* practically without leucocytic exudation

The phenomena do not end with macrophagy for despite the fact that focal inflammatory reaction has ceased parasites may again leave this focus to be disseminated throughout the body (the tissues have isolated these leishmanias by macrophagy but the parasites evolve and finally escape the cyst) and the cycle is renewed beginning with the first hematogenous flooding

Because of this fact in Chagas disease a periodic division of morbid states may be made The dual reactions mechanism of infection and endogenous reinfection differ fundamentally in the precise evolutionary movement of the disease process

The primary infection is a very severe attack multiple and simultaneous in many regions of the body which accounts for the seriousness of the infection In the second stage (chronic according to Chagas) the attack is more scattered and there are successive phases so that foci of infection do not exist simultaneously In addition although the cellular reactions are intense they have a changed quality The first inflammatory reactions are almost suppurative intensely exudative and necrotic (ulceration of the chagomas) The later inflammatory reactions are on the other hand more attenuated with more evident proliferation Special technics show that there is a greater specific parenchymatous injury than is true for the primary infection We see a condition quite similar to that seen in syphilis the later reactions are much less inflammatory than the primary or secondary but the parenchymatous lesions are more serious

The *primary period* is characterized by chagoma of inoculation neighboring adenitis reactive local and general adenopathy primary hematogenous dissemination and primary parasitic entrance into the tissues

When the local reaction of primary infection or primary localization (chagoma of inoculation or ophthalmoglandular complex) subsides there appear allergic signs the differential count and myocardial lesions are modified The latter primarily inflammatory now become complicated with alterations in the contractile fibers Thus the patient enters the *secondary period or secondary stage*, characterized by reinfection or by successive endogenous flooding of the system this period is the so called *chronic*" disease of Carlos Chagas

The *tertiary period* is understood to be that which is characterized by an intense fibrous reaction in the inflammatory foci It is the period of myocardial fibrosis in adults fibrous hepatitis etc

The most serious stage in Chagas' disease is the primary period when the first hematogenous dissemination followed by visceral invasion occurs The tissues are overwhelmed by an enormous number of trypanosomes and for this reason inflammatory reactions easily interfere with vitally important functions namely the heart and neuraxis or they may so alter the organic structure that the way is paved for later infection

Thus for example cardiac dysfunction of the primary period is accompanied by passive circulatory pulmonary stasis and by an increased fibrinogen (since it is increased in the blood during this inflammatory stage) Moreover endothelial lesions occur in the lung due to foci of trypanosomiasis all of which with fibrinogenesis and congestion form a fertile field for the development of secondary infection generally bronchopneumonic This is the secondary cause of death most frequently seen in children

In the *primary period* lesions of the central nervous system may lead to a serious meningitis Since specific inflamed tissues are subject to infection it follows that bacterial meningitis secondary to chagasic neuraxitis from the pathogenic point of view is a definite possibility

In the *secondary period* there are to be distinguished two fundamental forms of myocarditis, the dominant visceral lesion in the anatomicopathologic picture in all fatal cases following primary infection These are

1 The early sclerotic form with a picture of progressive myocardial fibrosis with very characteristic morphology

2 The early infiltrative form insidious in its development with rhythmic discharge of parasites into the circulation an anatomicopathologic complex in which are mixed inflammatory foci and extensions allergy secondary degeneration of contractile fibers and moderate sclerosis generally reticular

THE CONJUNCTIVA IN CHAGAS DISEASE IN FORMS WITH OPHTHALMOGLANDULAR COMPLEX

Acute primary conjunctivitis caused by *T cruzi* is a rare complication In much conjunctival biopsy material removed from patients with the ophthalmoglandular complex only a very small number of positives have been

month. However, he cited a case in which parasites were demonstrable in the blood for five months. The thick drop examination of the blood, method of Ross, as a laboratory procedure for the diagnosis of Chagas' disease, has enabled us to find trypanosomes in the circulation for seven to nine months or even longer. *With this fact, the designation "acute stage" has lost its* original meaning as generally understood in clinical practice.

Mazza and Jorg, in 1935, proposed calling the *primary period* or *primary stage* the period of time during which there are present external symptoms indicating the entry of the parasite (the designated *chagmoma of inoculation* or epiphenomenon "palpebral edema" which follows the already established chagasic infection or indicates, very exceptionally, entrance of the infection into the conjunctiva).

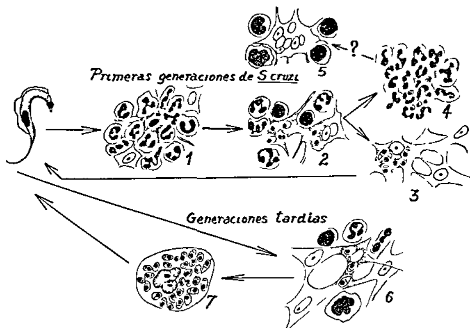


Fig 59.—Differences between inflammatory reaction of primary infection and the successive reactions through endogenous reinfection (After Mazza and Jorg.) (See Fig 58.)

In cases without appreciable external signs, the *primary period* comprises the entire time during which it is possible to demonstrate the parasites by means of simple microscopic examination of the blood. In the absence of trypanosomes, a rather common occurrence in affected adults, the first period is the time during which fever and tachycardia are present.

With the clinical regional polyadenopathy around the focus of *cutaneous primary infection* or *primary localization* (for example facial cellulitis with its characteristic one sided bipalpebral edema of the face) there is always found a gland with inflammatory reaction its size and the surrounding inflammation dominate other *affected glands in that zone*

Histologic study of glands of this character permit their classification as acute adenitis Because of their resemblance to the dominant gland in neighboring adenopathy found in syphilitic chancre ("prefect" gland of Ricard) Mazza and Jorg have designated it 'prefect' gland of *primary chagasic adenopathy*

It can be recognized by the deeply modified and totally obliterated glandular structure Lymphangitis and periadenitis are always found The cortical *zone of the gland is most deeply modified Follicular disposition is always* obscure The subcapsular lymphatic sinuses and primary perifollicular vessels are dilated and filled with the densest histiocytic proliferation The cortical follicles are masked by proliferation and infiltration or are indistinct They are very hyperplastic

The medullary portion is always indistinct and is transformed into monomorphous inflammatory tissue or is sclerosed

The glands can no longer be recognized as such the tissue being changed into dense mottled cellular residue *in which histiocytic proliferation* is always most intense it is compact or inserted sporadically among the remaining lymphatics or nodules or bands may be formed

Apart from this there exist foci of polymorphonuclear infiltration that show a true acute inflammatory aspect phlegmonous or furunculoid always localized in the cortical layer with multifocal necrosis of toxic character Around these foci there is observed hemorrhage with erythrophagy

This acute glandular inflammation is due to the great numbers of leishmanias of *T cruzi* present

Around the prefect gland with acute adenitis of Type I there is frequently found a group of glands enlarged inflammatory but with more at*tenuated manifestations than in the former case* Anatomically and clinically this is primary systematic regional adenopathy or gland lesion **Type II** of Mazza and Jorg (1938)

In these glands *the division between the cortical and medullary layers is* definite although the structure is profoundly altered In the cortical layer the follicles are much enlarged due to histiocytic hyperplasia which forms a clear center Around these there are other newly formed nodules of the same structure which thus fill the cortical layer in which appear bands and irregular masses of densely grouped histiocytes their growth displaces and separates the original lymphatic glandular tissue

The lymphatic sinuses of these glands are filled with dense cellular histiocytic proliferation analogous to the newly formed nodules in the cortical layer In a small number of these glands there are polymorphonuclear foci with small zones of necrosis containing leishmanias

found In these cases there were large numbers of leishmanias beneath the necrotic erosive zone of epithelium Polymorphonuclear infiltration was very dense and formed a layer in close contact with the epithelium but did not deeply invade the choroid

In much of the biopsy material *secondary conjunctivitis* predominated or better, *secondary inflammatory conjunctival reaction* of chagasic origin It is not of primary exogenous origin it is endogenous and is produced by spreading or extension of the neighboring inflammation Cellulitis spread by superficial lymphangitis was found in most of the cases or there was lymphangitis or direct spread of deep inflammation arising from Tenon s capsule or from the cellular orbital tissue

Lesions most commonly found are edema of conjunctiva and choroid and capillary and venous global congestion Extravasation of blood is infrequent

The most important lesion is a subepithelial infiltration with lymphangitis Infiltration consists of plasmocytes exclusively or a few lymphocytes

In a small number of cases the infiltration alone or with a concomitant histiocytic hyperplasia forms nodules which are always subepithelial In somewhat more than half the cases are found foci of intense histiocytic proliferation In a fourth of all conjunctivas histologically examined there were found within the foci of infiltration giant cells (histiocytic plasmodia) Almost invariably their presence coincided with the presence of leishmanias although these generally are not contained within these polykaryocytes

In a certain number of cases the subepithelial lesions are the most recent and present less of an exudative character than those more deeply situated In these cases it is possible to establish that the lesion has advanced from the base to the surface Within the depth there are frequently found gigantic cellular follicles and leishmanias whereas near the surface there is scarcely to be seen a moderate plasmocytic or lymphoplasmocytic infiltration

These cases demonstrate clearly that here is secondary inflammatory conjunctival reaction coming from within toward the surface

GLANDULAR FORMS

Lymphatic Glands — Anatomicopathologic examination of lymphatic glands extirpated from patients at different periods of Chagas disease has enabled Mazza and Jorg to define three fundamental types of glandular lesion designated as Types I II and III

Type I, hereafter referred to as *acute chagasic adenitis* is the most typical and specific of the glandular lesions and is characterized by acute microabscesses necrosis and the presence of many leishmania forms This form of adenitis individualizes the glandular reaction to the manifestations of evident cutaneous portal of entry (chagoma of inoculation) narrows it to cutaneous primary localization in cases in which the portal of infection cannot be seen or where there is no inflammatory manifestation and finally it limits it to primary lymphatic fixation in the septicemic period of Chagas disease without previous adenitic lesions

In fatal cases the dominant lesion is cardiac There is acute myocarditis localized immediately below the epicardium becoming attenuated as it advances toward the endocardium The epicardium intensely infiltrated in some cases shows fibrinous villosities There is always a small quantity of fluid in the pericardium indicative of acute inflammation The endocardium although less affected shows inflammatory foci which reach the muscular spindles At times the conduction system is also affected

Lesions of cardiac fibers as such vary as much in intensity as in other characteristics However in clear cases of pure chagasic deaths there exist regressive alterations in muscular fibers sometimes in the form of very extensive simple inflammatory atrophy sometimes in more varied degeneration waxy grumous or hyaline

In fatal Chagas disease of long duration (ten to twenty years) the dominant lesion has always been cardiac and with the same subepicardial localization as in the acute fatal cases There is observed in these cases fibrinous epicarditis and simple endocarditis with greater intensity and greater sclerosis than are seen in the first period

In such cases the inflammatory lesion of the myocardium develops all the lesions observed in the first period' deaths there are foci at all ages and in the most varied phases of evolution Besides acute infiltration there are found giant cell foci and zones of sclerosis which indicate that chronic myocarditis is present with alternating acute changes or foci of acute inflammation Many of these foci resemble forms found in other chronic infectious diseases

There exist too lesions of the muscle cells sometimes in the form of granulogrumous myomalacia with invasion of macrophages sometimes in the form of degenerative lesions of the striated fibers

The special characteristic of these cases is the periodic renewal of acuteness of the affection we are dealing with an inflammation with perpetual renewal insidiously undermining the myocardium with localized regressive irreparable alterations These patients have an acute myocarditis that increases in severity until death occurs

Hepatic lesions are variable There is frequently steatosis (yellow liver similar to that of yellow fever) and nodular foci of histiocytosis often with leishmanias (Mazza and Jorg) This last type of lesion prompted Mazza to search for it by hepatic viscerotomy in cases of sudden death especially in infants

Acute splenitis with incipient fibrosis is the most characteristic lesion of the spleen as is histiocytic proliferation of the germinal centers of the Malpighian follicles in relation to glandular lesions which we have designated as **Type III**

Changes in the brain are focal corticoencephalitis with proliferation of larger cells and perivascular infiltration and proliferation neighboring inflammatory changes perineuronal acute meningochoroiditis especially in cases of toxic impregnation of the neuraxis and neuraxitis without demonstrable parasites in the nervous tissue

This is the lesion of *attenuated chagasic adenitis* with a high degree of intrafollicular histiocytic hyperplasia It is intrasinusal and corticonodular When this histiocytosis, sinusal or in bands is very greatly disseminated, it may reach the point of reproducing classical *adenitis with clear areas as a residuum of the postinflammatory hyperplastic state of the gland* This is Type III of Mazza and Jorg which these authors later designated as *generalized secondary polyadenopathy* This appears simultaneously with or following regional adenopathy in relation to lesions of mucocutaneous primary infection or primary localization It corresponds to macropolyadenopathy characteristic of the tertiary form of Chagas' disease

These lesions are absolutely nonspecific and are found in glands removed from various regions of the body They are simple reactive cellular hyperplasias with intense histiocytosis in sinusal and follicular epithelioid cells

Lacrimal and Salivary Glands—These are often affected *Chagasic dacryoadenitis* of the lacrimal gland studied at biopsy of the palpebral prolongation of the orbital gland is composed of zones of glandular parenchyma with scant infiltration surrounded by a large inflammatory zone which separates and destroys glandular tissue There are acute inflammatory granulomas with marked histiocytic pattern with a predominantly lymphocytic infiltration within them the confluence of histiocytes forming multinuclear *plasmodia*

The second type preferably studied in parotids with accompanying gland biopsy, is a lesion carried through the lymphatics or by direct progression There almost always exists a large inflammatory focus poorly defined surrounded by an unaltered gland In the midst of this there are found leishmanias in reduced numbers as in the lacrimal gland

The *chagasic sialoadenitic lesion* is not the same as a bacterial lesion since only the cortical part is involved the center of the gland remaining undamaged This lesion also differs from tuberculous sialoadenitis by reason of the existence of polymorphonuclear leucocytic inflammatory elements by the absence of caseation by the presence of histiocytic follicles surrounding the giant cells and finally by the presence of leishmanias

Skeletomuscular—*Acute parasitic myositis of Chagas' disease* while frequent in animals is nevertheless rather difficult to verify in man In biopsy of muscle in the first period of Chagas disease there have been found rather regularly foci of necrotic myositis In this are seen fibers infiltrated at times with *polymorphonuclear cells at times with lymphocytes and plasmocytes* exceptionally with giant cells in the midst of healthy muscle tissue The invaded muscle segment undergoes necrosis or shows fragmentation These foci correspond to foci or zones of residual infiltration this in turn corresponding to primary parasitic myositis

Even though the muscle biopsy (punch biopsy) does not from the viewpoint of parasitology constitute definite diagnostic proof it does form a basis for a valuable anatomicopathologic estimate for recognition of the nature of the disease since there are no other affections which form such limited foci of monocellular alteration

The so called chagomic zone is generally surrounded by a wide hard elastic edema which does not pit on pressure

In the center of this ligneous area there may be a reddish hemorrhagic point with rose colored margins The erysipeloid outer surface of the chagoma generally shows a thin *furfuraceous desquamation*

With infants up to 1 year of age demonstration of *T cruzi* in the blood offers no difficulties and assures the diagnosis *In older children adolescents* and adults finding the trypanosomes by microscopic examination is more difficult and requires repeated periodic examinations for several days



Fig 60—Right temporal *chagoma of inoculation* with edema of both eyelids and the corresponding half of the face tenth day of development

If the examination of the blood gives negative results and if splenomegaly and more constantly hepatomegaly are present as well as definite signs of myocarditis as seen in the cardiac shadow upon teleroentgenography especially of the left ventricle with disappearance of the first sound in the mitral area and intermittent pulse one should resort to other diagnostic measures such as *xenodiagnosis* and *inoculation of blood* into white rats Both procedures however require a minimum of twelve to twenty five days before definite results become available

In difficult cases the differential count aids greatly in the diagnosis especially when there is a high *monocytosis* in children or a very high *lympho*

Lesions of *meningochoroido corticoencephalitis* are much the same as lesions of encephalitis in trypanosomiasis africana But lesions of chagasic corticoencephalitis are more frequent with many parasites present (leishmanias) In the vascular endothelium of venules and in perivascular cells leishmania forms are found (Mazza and Jorg) These are also present in nodules in the midst of nervous tissue In these nodular formations microglia cells as well as leucocytes intervene

As for *chagomas of inoculation* tumor like lesions from the cutaneous entry of chagasic infection these present histologically characters of most intense erosive pseudoulcerous dermoepidermitis with hypodermic *cytosteatonecrosis*

Metastatic chagomas appearing in the neighborhood of the chagomas of inoculation as if there existed a multicentric process of cutaneous tumor like manifestations are located in the skin with *inflammatory cytosteatonecrosis of* subcutaneous cellular tissue

Hematogenous chagomas are of the nature of cellulitis or dermatic hypodermatitis of hematogenous origin with different apearance in respect to tumor like phenomena of inoculation These chagomas histologically show cellulitis with *cytosteatonecrosis* Extension of the inflammatory lesions to the dermis is slight One variety of these chagomas is the *lipochagoma* (Mazza Freire) which is a localization of the trypanosomic inflammation in the adipose tissue of the cheeks In these cases the profound cellulitis of hematogenous character is histologically always inflammatory cytosteatonecrosis

SYMPTOMATOLOGY AND CLINICAL FORMS OF THE PRIMARY PERIOD OR FIRST STAGE OF THE DISEASE

In the first stage or primary period Chagas disease may or may not present external signs The most common external manifestations are as follows

1 Chagomas of Inoculation (Mazza) also called Cutaneous Glandular Complex (G and R Basso)

These may occur in any part of the body but they are seen most frequently about the head and face especially the forehead the neck the cheeks and the lip They are characterized by plaques of peculiar pasteboard like hardening of the skin not pliable generally hot and red which appear as if etched into the skin When formed in the abdominal wall and thighs these chagomas may assume large proportions They then cause hard ligneous infiltration which makes it impossible to bend the lower limbs They cause great pain There is generally multiple adenopathy with one very large gland predominating There is an elevation of temperature usually high in infants A sign of major diagnostic importance is tachycardia out of all proportion to the fever and fever may even be absent General malaise exhaustion osteo muscular pains and sometimes epistaxis and chills together with insomnia and restlessness and in nursing children continuous crying may occur either simultaneously or successively as manifestations of the *chagoma of inoculation*

cytosis at other ages accompanied by a more or less marked eosinophilia This may occur in the first stage or primary period

The chagoma of inoculation if left alone progressively disappears usually in two or three months Brown pigmentation which persists at the site of the lesion is most characteristic *There is atrophic retraction of the* skin the latter remaining adherent to the deeper planes of the chagoma as if fixed by *fibrous bands due to disappearance of the underlying fatty tissue*



Fig 63 —Left antebrachial chagoma of inoculation *I* and metastatic chagomas in left axilla *(arrows)*

and even of the smooth and striated muscles This effect is more perceptible when the chagoma is localized in the cheeks for when Bichat s pad because of its contiguity is involved it gives rise to *genial lipochagoma* (Mazza and *Freire) of the affected side* The consequent cytosteatonecrosis causes a fibrous retractile formation of the lipophagic granuloma In hairy areas alopecia is observed after the disappearance of the chagoma

By metastasis the fatty pad of Bichat may be invaded on the side opposite the infected area



Fig 61 —Chagoma of inoculation in the neck of a 6 month old child sixth day of development



Fig 62 —Edema of left eyelids (ophthalmoglandular complex) in the patient shown in Fig 61 in the sixth day of the chagoma of inoculation Shows absence of conjunctival contamination

The conjunctiva of the affected sides remains unaffected in certain cases, in others there is intense injection and edema chemosis and marked epiphora Suppuration seldom occurs Empirical medication is of no avail Generally seromucous secretion glues the eyelashes together In well established cases where the conjunctiva resembles that of Parinaud's conjunctivitis granulation changes and inflammatory products can be noticed in both lids especially the lower

The lacrimal sac may in certain cases suppurate and give the appearance of dacryocystitis but only in Chagas' disease is it accompanied by fever general exhaustion especially by tachycardia which may occur even without fever



Fig 64



Fig 6

Fig 64 Left ophthalmoglandular syndrome or complex thirteenth day of development (front view)

Fig 65 —Chagoma of inoculation in the check giving an impression of left ophthalmoglandular syndrome This is a very common pseudopalpebroglandular complex. This complex is rarely observed in its pure form

This last symptom which denotes myocardial affection is the most important differential point by which to distinguish true Chagas' disease from various common conditions which may simulate it In very young children this symptom with bronchitis and a very severe diarrhea is very frequently found

Exophthalmia usually occurs in conjunction with unilateral and erythrochromic edema of the eyelids with or without deviation of the eyeball. This is very pronounced in some cases not reducible because of the orbital cellulitis clearly showing its endogenous origin

These *metastatic chagomas* appear also in regions that are more or less symmetrical with those of the chagomas of inoculation, and they, too, undergo necrosis and formation of scabs They may also be seen in cases which had previously shown an apparently initial ophthalmoglandular complex

But the important chagomas are those which we have designated as *hematogenous* They occur in patients without any previous outside portal of entry of infection They have a characteristic appearance especially in infants They are consistent, hard formations which can be palpated under the skin by skin compression, in some cases without change in color, or in other cases revealing erythematous zones, characteristically indurated, so that these areas are very tough, with loss of cutaneous pliability

These hematogenous chagomas generally disappear leaving no effects of a permanent nature other than damage to that part of the skin where they were situated They may become soft and form abscesses, giving the clinical impression of a septicopyemic state The abscesses may be located symmetrically

The chagoma of inoculation may run another course, namely, that of ulceration In such cases, the lesion is covered with melicerous crusts or scabs which, when removed, reveal a granular surface that bleeds slightly, displaying a marked analogy to the lesions of cutaneous leishmaniasis

These ulcerations generally heal in a short time even without treatment leaving, after two or three months, cicatrices which though appreciably small, are definite in size and usually hyperpigmented

2 Unilateral Palpebral Edema Ophthalmoglandular Complex (G and R Basso), Palpebrofacial Cellulitis (Mazza and Jorg)

This is a frequent manifestation attributed by some to entry of infection into the conjunctiva However, it often occurs in individuals with previous general infection of several days' duration it may also follow trauma of the orbital region (fisticuffs) In many cases, edema of the eyelids is due to chagoma of inoculation in this region, at the base of the nose, or in neighboring areas and this cutaneous inoculation does not apppear immediately

Again, there is the question of edema of both eyelids which in general, arises suddenly and is usually noticed by the patient on awakening in the morning In this condition there is a violet red or livid coloration of the ocular adnexa The edema is usually very firm and does not yield to pressure, it advances rapidly toward the cheek the base of the nose, and the temporal region and extends to the neck and down to the supraclavicular fossa

Generally it is not painful even on pressure, but it may be hot the skin over the eyelids usually shows a furfuraceous desquamation

The preauricular or pretragal gland of the affected side is usually swollen to a noticeable degree It may be as large as a pigeon s egg or an olive, with or without periadenitis, frequently accompanied by minor neighboring adenopathy These glandular enlargements are particularly noticeable in the submaxillary or parotid regions This with the edema, considerably alters the appearance of this area

eyelids which was originally unilateral now spreads Finally, anasarca may follow these original manifestations

But these edematous symptoms may also be found often without preceding phenomena or apparent signs of infection apparently arising from some unknown point of entry

Among the most frequent of these primary edematous manifestations may be mentioned edema of the scrotum common in male infants edema of the pubis and lower abdomen in female infants areas of edema in both legs and thighs edema which we have designated "grotesque" because of its appearance in midbody or in one limb only or on the forehead



Fig 66



Fig 67

Fig 66—Pronounced exophthalmia. Twenty-seventh day of development of chagoma of inoculation in the left upper lid

Fig 67—Anasarca in a girl who was considered fat by her parents With no known previous portal or entry

In all these cases after excluding the possibility of genuine kidney disease if macropolyadenopathy and hepatosplenomegaly are present and particularly if there are signs of myocardial disturbance revealed at times only by tachycardia especially with fever these should induce a search for *T cruzi* in the blood especially in those geographical zones known to be endemic regions of Chagas disease

CHAGAS DISEASE WITHOUT EXTERNAL MANIFESTATIONS

In addition to these definite forms of Chagas disease described above which suggest the diagnosis even to inexperienced workers or influence one to resort to proper microscopic examination there are other cases which re

In untreated patients *palpebral edema* like exophthalmia may persist for four or even seven months

Another valuable and striking symptom especially in patients with a pre existing ophthalmoglandular syndrome is *dacryoadenitis chagasica* (Mazza and Benitez)—a point to be remembered in summing up the diagnosis We have designated this as hyperplasia and congestion of the palpebral or ac cessory lacrimal gland It may be determined by elevating the external part of the upper eyelid with the fingers and having the patient look downward and inward

This symptom of dacryoadenitis chagasica is slow to disappear and often persists after the palpebrofacial edema and other signs present in the sec ondary conjunctival reaction have subsided

At times the unilateral edema of the eyelids shifts to the opposite side more rarely it may exist simultaneously in both eyes

At any rate in the absence of albuminuria in these last cases bilateral and other diffused pretragal or submaxillary adenopathy as well as tachy cardia hepatosplenomegaly and great exhaustion accompanied by somnolence and in infants by signs of meningeal irritation offer clinical evidence in the diagnosis of Chagas' infection

3 Schizotrypanides

This refers to skin manifestations of chagasic origin so designated be cause of their analogy to trypanides of sleeping sickness or trypanosomiasis africana In Chagas disease there are different types

(a) *Morbilliform* not accompanied by the same essential signs of genuine measles It does not spread to the face There are no high temperatures It is not contagious for other children Koplik s spots are absent Patients who have had measles may be affected and the sickness may appear at other than epidemic periods

(b) *Urticariform* generally not pruriginous followed by persisting zones of brown hyperpigmentation

(c) *Multiform erythematous* the outbreaks of various size located prefer ably on the anterior surfaces of the thorax and thighs rarely diffuse

(d) *Ulceration* which may appear late

All of these schizotrypanides may follow manifestations of this infection such as chagomas or the ophthalmoglandular complex or they may be followed by these last named symptoms They cause elevations of temperature at the time of eruption and may persist for several days disappearing finally with out complications

4 Localized Edema, Anasarca

This edema is very firm elastic without crepitation frequently follow ing chagomas of inoculation or the ophthalmoglandular complex It localizes in the legs and feet sometimes ascending to the pubic and lower abdominal regions The face usually remains swollen due to the fact that edema of the

ence of *T cruzi* is shown by its dancing movements scarcely moving out of the field of view This procedure is particularly useful in examination of nursing infants where generally a large number of parasites are found in the circulating blood In older children adolescents and adults diagnosis in this manner can be made less frequently

The *thick film* examination is of great value The film is stained with Giemsa stain without previous fixation In this procedure a dilution of one drop of stain for each cubic centimeter of neutral distilled water is placed on the thick film which has been dried in the air The erythrocytes are hemolyzed leaving the white blood cells blood platelets and the parasites properly stained

This test should be repeated periodically or every day making several preparations each time and examining each carefully *T cruzi* in the bloood can usually be demonstrated with this method Sometimes it is necessary to stain *five or six thick drop preparations* before arriving at a definite diagnosis

If this test fails to reveal the parasites it is necessary to rely on injection of 0 5 c c to 0 75 c c of citrated blood intraperitoneally into white rats If the result is positive trypanosomes will appear in the blood after a period of five to twelve days and sometimes after twenty to twenty five days

This method is to be used for relatively recent cases and for children For older patients with a longer development of the disease injection intraperitoneally of 5 to 10 c c of citrated blood is indicated Up to 20 c c of citrated blood can be conveniently injected intraperitoneally into puppies about 1 month old to demonstrate cases during the tertiary period especially cardiac cases Observation of these animals should extend over a period of three months with periodic examinations of the blood Even though the blood examination is negative a complete histopathologic examination of all the organs and skeletal muscles of the inoculated animal must be made

It should be noted that animals which do not show trypanosomes in the circulation during life may nevertheless present leishmanias of *T cruzi* either in the striated muscles or in the smooth muscles of the stomach and intestine or in the heart or even in the skin or subcutaneous cellular tissue (Mazza)

Xenodiagnosis

(See Chapter 72)

Biopsy

Biopsy of lymphatic glands with proof of leishmanias in the histologic section is a procedure which should follow those just explained namely the extirpation of the so called prefect gland Biopsy or punch biopsy of striated muscle is of little value because poor results are usually obtained in demonstration of leishmanias

Residual lymphocytic plasmocytic infiltration with giant cells in necrotic and fragmentary muscular segments may give well founded indications of Chagas disease even in the absence of parasites

quire the services of trained observers to recognize the possibility of their existence in endemic rural areas greatly infested by triatomas which harbor the developing forms of *T cruzi* In such cases, there is scant evidence of this infection, so that many of the cases may escape detection

Of importance in the diagnosis of all cases is the appearance of cardiac changes, especially alterations in rhythm, with lowering of arterial tension especially embryocardia in infants, or tachycardia of high frequency at other ages These signs and symptoms, together with hepatosplenomegaly and multiple adenopathy, should suggest an examination of the blood for *T cruzi*

With no previous external signs, the most important manifestation of Chagas' disease is *primary meningoencephalitis* It affects nursing infants exclusively and may be very serious, as a matter of fact, it is almost always fatal

We have used the term *primary* meningoencephalitis because this localization may also occur *secondarily* in the course of the disease with such initial manifestations as chagomas of inoculation, ophthalmoglandular complex, edema, anasarca, etc

Convulsions are usually solitary and infrequent in other cases, however, they are generalized, clonic or tonic and preceded by great unrest and persistent and inconsolable crying The convulsions at first are not of a serious character They later become more frequent of longer duration and often show a tetanic character, with opisthotonus repeated vomiting of the cerebral type, and constant crying

These clinical forms are of short duration, and in general death may follow *in less than a week Few survive this stage without due treatment* According to Chagas, such patients show serious nervous syndromes which probably, until Chagas described them, were thought to be the result of some other disease

Those who recovered under adequate treatment, as far as is known, showed no sequelae or residual effects of the invasion of the central nervous system

Forms that are simply primary febrile or which are accompanied by the typhoid or tuberculosis like state certainly are often overlooked in endemic regions

It is of great diagnostic importance in such cases to evaluate the temperature curve, for example, a rise of 2 or more degrees in twenty four hours, when the temperature is taken every three hours This phenomenon in which respect Chagas' disease resembles visceral leishmaniasis is not constant and may be replaced by a frank notching of the peak of the evening temperature rise in Chagas' disease, it is explained by the greater or lesser invasion of the organs by the leishmania forms of the parasite

ETIOLOGIC DIAGNOSIS

In all cases where Chagas' disease is suspected, it is essential to demonstrate the chagasic etiologic character of the disease This test can be made by direct examination of fresh blood between cover glass and slide Pres

appreciable clinical improvement (reduction of edema glandular enlargement decreased tachycardia cephalalgia fever restlessness somnolence), it is best to administer the drug only every other day or at two day intervals

For adolescent and adult males a minimum of 0 ?0 to 0 60 Gm per kilogram of body weight should be reached 0 20 to 0 40 Gm is used for women

In nursing infants especially those with the meningoencephalitic form it is necessary to arrive at and to administer as quickly as possible a minimum dosage of 120 to 1?0 mg per kilogram and even more than this amount according to the severity of the case

It is desirable to repeat the administration of 7602 (Ac) *(Bayer)* or M 3024 *(I C I)* after a short period of rest 7602 (Ac) *(Bayer)* and M 3024 *(I C I)* have no action against other trypanosomes *9736 (As) (Bayer)* has been used in Chagas disease by Mazza with good clinical results

Dosage of 9736 (As) (Bayer) is as follows for children doses of 15 c c up to a total of 30 c c for male adults 50 c c and women 40 c c total doses are given

Sodium penicillin shows pronounced clinical action in doses of 20 000 to 30 000 Oxford units per kilogram of weight It is given intramuscularly in injections of 10 000 to 20 000 units every three hours Its trypanocidal effect however is low

In every case the patient is to rest preferably in bed confined to his home and must avoid hard work that may adversely affect the action of the heart

If cardiac tonics are necessary they are to be used with caution Administration of vitamins especially of the B group (thiamine hydrochloride) intramuscularly and in appreciable dosage is more beneficial Liver extract especially with vitamin B or even used alone causes improvement many times in the majority of patients In addition this therapeusis favors greater toleration of other drugs

Certain arsenicals such as cacodylates Sulfarsenol neoarsphenamine arsphenamine Acetylarsan Pirossyl (Stovarsol) *may be conveniently used* for although they lack specific action against the disease they have a general tonic effect stimulating the reticuloendothelial system and they also act upon a concomitant hereditary or acquired syphilitic lesions

When these drugs fail water soluble salts of bismuth may be used administered as for syphilis

PROPHYLAXIS

Prophylaxis consists in avoiding contact with vinchucas or kissing bugs" as the triatoma transmitters are called Since these breed in primitive or lowly dwellings it is through construction of adequate housing that the vector will eventually be exterminated a very difficult problem in sparsely populated regions or in districts with great poverty

The complement fixation reaction or the Guerreiro Machado reaction, applied to Chagas' disease, with serum of the patient in the presence of aqueous extract of liver from a puppy which has died of the disease, gives results of great presumptive value It is particularly indicated in the secondary and tertiary periods of the disease While the test may be positive, it still does not entirely exclude the necessity of inoculating the patient's blood into susceptible animals, nor does it exclude the use of xenodiagnosis

These tests as well as cutaneous and intradermal tests by themselves do not assure a definitive diagnosis of Chagas' disease They may simply indicate an old infection by *T cruzi* This is not unusual in localities where often all the inhabitants have overcome the chagasic infection at one time or another

TREATMENT

In our experience medication which has proved efficacious against other forms of trypanosomes has had no effect against *T cruzi* Various arsenicals have been tried, one after the other without success notwithstanding the fact that they are effective against other trypanosomal infections in man and in lower animals

In 1936, a preparation known as *7602 (Ac) (Bayer)* was developed by Jensch of Leverkuffen The composition of this drug a *quinoline derivative,* was described by Curd in England in 1945 (Mazza 1945) It is a *sulfate of diallyl malonyl diamide of 2 methyl 4,6, diamino quinoline*

Curd also synthesized a product called *M 3024 (I C I)* Fulton (1943) showed experimentally the similarity of its effects with the original German drug Mazza showed that *M 3024 (I C I)* has the same action and clinical efficacy as *7602 (Ac) (Bayer)* This substance mixed with twice its weight of urea, is used as a solution prepared at the time of use It is made by dissolving 0 15 Gm of sterile powder, which is kept in sealed ampules in 5 c c of doubly distilled water (3 per cent) and is injected intramuscularly deep into the buttocks, using a fine needle

The injection causes pain Greater dilution does not prevent pain nor does it avoid discoloration at the site of injection persisting for one or two days

Following each treatment there is frequently a rise in temperature There also develops unrest and malaise in addition to a brief increase in external symptoms in the twenty four hours following the first injection

Injections may be repeated daily in the referred dosage of 0 15 Gm and may even be doubled or tripled (0 30 Gm or 0 45 Gm in 10 c c or 15 c c of water respectively), always preceded by a test for albumin in the urine If albumin is present it is desirable to wait until it disappears, if however, the injection is urgently needed, the size of the dose may be decreased

In general after albuminuria disappears it does not reappear when treatment is resumed provided there have been four or five days of rest After

CHAPTER 9

AFRICAN SLEEPING SICKNESS

Oscar Felsenfeld

Sleeping sickness or African trypanosomiasis is often designated as "African sleeping sickness," to distinguish it from Economo's lethargic encephalitis which also formerly was called "sleeping sickness." It is a disease caused by trypanosomes and is characterized by chronic fever, more or less intensive glandular enlargement, and, in many cases, a cerebral stage with fatal outcome.

GEOGRAPHY

The geography of sleeping sickness follows the African belt of the tsetse flies (Glossina), mainly of *Glossina palpalis*, *Glossina tachinoides*, *Glossina morsitans*, and *Glossina swynnertoni* which are the most frequent insect vectors of the disease. The northern boundary of sleeping sickness today approximately follows a line drawn from St. Louis to the Lake Chad, then along the Shari and the southern part of Anglo-Egyptian Sudan. Abyssinia and Italian Somaliland are free from it. South West Africa and the Zambezi River, with the exception of two foci, are the southern boundaries, while in West Africa, along the Gulf of Guinea, in the Congo, in Angola, Sudan, Uganda, and Kenya, the classic type ascribed to *Trypanosoma gambiense* prevails and the Rhodesian type ascribed to *Trypanosoma rhodesiense* is found in Tanganyika, Mozambique, Nyasaland, and Rhodesia.

Etiology

Sleeping sickness is caused by trypanosomes. These organisms are very similar to *Trypanosoma brucei*, the agent of the animal disease "nagana." Two types of trypanosomes have been described as the cause of sleeping sickness: *T. gambiense* and *T. rhodesiense*. It is not possible to differentiate between these types morphologically or by animal experiments, except by production of keratitis in goats by *T. rhodesiense*. It was formerly believed that the forms of *T. rhodesiense* in the blood of injected mice or rats more frequently have their nuclei located more posteriorly than do forms of *T. gambiense* under similar experimental conditions. Some authors consider *T. rhodesiense* a human-adapted variant of *T. brucei*. Others ascribe the difference in clinical types of sleeping sickness to the adaptation of the trypanosomes to different species of Glossina.

The organisms appear irregularly in the blood but are usually present during the periods of fever. They are most easily found in enlarged lymph glands, later occurring in body fluids, principally the cerebrospinal fluid. Aside from elongated, slender trypanosomes, rather short, broad forms with smaller flagella and posterior nuclei may be observed. After the organisms enter the tsetse fly by feeding on a patient who harbors trypanosomes, they multiply in the mid gut, later in the hind gut, of the Glossina. After twelve to thirty six days, depending on temperature, humidity, and other factors, the infective metacyclic forms reach the salivary glands of the fly and may be injected into a susceptible host during a blood meal.

Trypanosomes of sleeping sickness are difficult to cultivate. They are, however, easily transferred to laboratory animals, chiefly to mice, rats, and guinea pigs.

As to personal hygiene, one should avoid placing bedding on the floors or having beds against the walls Sleeping with mosquito netting stretched well away from the body and with the lights kept burning are also highly recommended

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to step on thin roots *T. rhodesiense* is found in the waterbuck *(Kobus ellipsoprymnus)* reedbuck *(Redunca arundinacea)* and duikerbok *(Cephalophus grimmi)* Cattle goats sheep and even pigs have been found to harbor trypanosomes

RESISTANCE

There is no racial predisposition to sleeping sickness Neither does the disease prefer people of one sex or of a certain age group Those who live near rivers or spend time working or travelling on inland waters are more exposed to the bite of tsetse flies and, therefore fall prey more easily to sleeping sickness

Trypanosomes as a rule are not transferred from the mother to the fetus Exceptions however have been described

There may be a certain degree of immunity among people who live in territories which have been infested for a long time Manson Bahr (1915) emphasized that sleeping sickness is less virulent in West Africa where it has been present for a very long time while in the newer foci of Uganda the course is more severe Due to the lack of partial immunity the disease is more acute in white men than in natives The Rhodesian form, however, is generally acute both in whites and in natives

PATHOLOGY

The bodies of patients who have died of African sleeping sickness are emaciated Since this is due to lack of nourishment the organic findings are with the exception of the central nervous system and the lymphatic apparatus rather meager

The skin may show edema which as a rule is confined to the face and the perineal region The back is less often involved The disease is principally an affection of the lymphatic system so that lymphatic infiltrations are often found in the skin

The lymph glands particularly of the neck of the mesentery, and of the groins are enlarged There is increased production and proliferation of the lymph cells The glands appear vascular In addition to the lymphocytosis monocytes are often found

The brain shows changes resembling those found in general paresis There is a chronic meningoencephalitis and a meningomyelitis The changes in the brain predominate The vessels are contracted Endarteritis with endothelial proliferation causes thickening of the vessels The perivascular space shows round cell infiltration Lymphocytes, neuroglia, and more or less modified plasmocytes form the infiltrate When perivascular infiltrates attain considerable width, they are called "coat sleeve" or "cuff"

The surface of the brain shows flattened convolutions and shallow sulci The brain tissue is edematous The ventricles are dilated by the pressure of the increased amount of cerebrospinal fluid The Rhodesian types show little changes in the brain

The cerebrospinal fluid contains many mononucleated cells such as lymphocytes, monocytes and plasmocytes Eosinophiles may also be present Trypanosomes can be found in many cases The total number of cells is 50 to 5,000 in fatal cases There is a great increase in the protein content, which may be higher than 1 5 Gm

VECTOR AND ANIMAL RESERVOIRS

The trypanosomes are usually transferred by tsetse flies after they have gone through a cyclic evolution in these insects There is, however, a possibility of purely mechanical transfer by Glossinae and other biting insects from person to person under certain circumstances

The principal species of Glossina which transfer sleeping sickness are *G palpalis* and *G tachinoides* for *T gambiense*, *G morsitans* and *G swynnertoni* for *T rhodesiense*

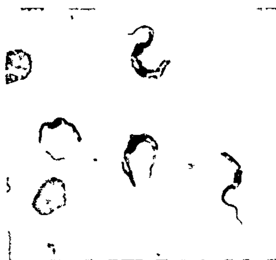


Fig 68 —*Trypanosoma gambiense* in peripheral blood

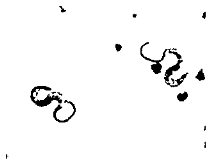


Fig 69 —*Trypanosoma rhodesiense* in peripheral blood

Most species of Glossina require shade and proximity of water *G palpalis* prefers human blood, while *G tachinoides* is impartial in its feeding habits *G morsitans* and *G swynnertoni* feed mostly on cattle and antelopes *G morsitans* is attracted by individuals, animals, and objects and will follow a running person or antelope for hundreds of yards

Glossinae which live in southwest Arabia are not infected with trypanosomes It is also worthy of note that the organisms are not transferred to the larvae of the flies

No repellent effective against tsetse flies is known

Of the animals naturally infected with *T gambiense*, the best known is the marsh inhabiting sitatunga (*Limnotragus spekei*), a shy antelope with highly cleft hoofs enabling it

Glomerulonephritis is not rare The spleen is not considerably enlarged There is round cell infiltration The number of Malpighian bodies is reduced As a rule the liver is not enlarged Pericardial, pleural and peritoneal effusions are common in the Rhodesian form

The heart shows round cell infiltration and degenerative changes Very intensive inflammatory alterations are common in the Rhodesian type The lungs may show proliferation of round cells The bone marrow shows regressive changes

Because the immediate cause of death is some intercurrent disease such as pneumonia malaria tuberculosis dysentery etc the autopsy findings are often *dominated by the changes caused by the terminal complicating sickness*

INCUBATION PERIOD

The incubation period is very irregular An incubation of ten to twenty one days is very often observed, *frequently, however, it is far longer* According to some authors the incubation period may be as protracted as several years

SYMPTOMATOLOGY

Classical Type

The initial phenomenon is the so called trypanosome chancre This consists of a red nodule surrounded by a pale zone The nodule is slightly elevated and attains a diameter of one half to one inch Its site is the place of the bite of the tsetse fly After a few days usually after three the nodule disappears leaving a slightly pigmented spot which may be visible in white patients for a few weeks

The first general symptom is the initial fever which develops one week or later after the initial chancre It is irregular, intermittent and remittent *courses are observed* While the morning temperature is normal or slightly subnormal the evening temperature may reach 103° to 104° F The decline of the fever is rarely accompanied by the usual sweating of such states

The pulse rate and the respiration rate increase with the height of the fever The patient complains of headache Neuralgia is often present The nerves of the extremities and of the head are most often involved *The pain* may be continuous or it may appear in attacks of varying intensities

A rash composed *of pinkish circinate nummular erythematous* skin lesions is observed in white patients The rash is often accompanied by pruritus and edema In the native population the erythema is scarcely visible because of the dark skin This rash disappears after some time

Trypanosomes appear in the blood during this period of the disease They are more abundant during the fever periods

Kerandel's sign is of much diagnostic value during this stage of the sickness This sign is based upon *the development of deep hyperesthesia* especially over the ulna A slight impulse which under normal conditions

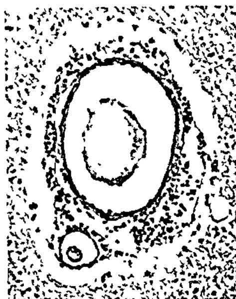


Fig 70 —Perivascular infiltration in the brain in sleeping sickness



Fig 71 —Meningitis in sleeping sickness high power

Very often the patient does not speak at all if not questioned The gait is deliberate and slow, as are the other movements Later the patient is scarcely able to keep awake and falls asleep even while eating There is loss of control of saliva urine, and stool

The habits of the patient deteriorate He becomes negligent and unclean Delusions and mania are often observed

Debility is a constant development *The facial expression reflects the* psychologic state It is dull and vacant The eyelids are lowered The lower lip begins to hang Saliva drips from the corner of the partly open mouth

The neurologic symptoms are governed by the localization and extent of the cerebral and meningeal lesions Headache, usually dull frontal or occipital pain rarely migraine like attacks is the rule Convulsions may be present Paralysis of nerves or groups of nerves is not uncommon

Fibrillary twitchings of the tongue and of the muscles of the arm are early symptoms of the cerebral stage Tremor of the tongue of the fingers and of the upper extremities rarely of the legs is very frequent from the beginning of sleeping sickness

Pruritus is a regular symptom causing scratching with subsequent skin infections

The knee jerks are increased in the beginning later decreased All reflexes are decreased during the later stage of the sickness

Because of the diminished ability of the patient to feed himself cachexia develops Symptoms of avitaminosis skin lesions and decubitus are very frequent

The cause of *death is an intercurrent disease as pneumonia dysentery or* injury also attack by animals mainly when the patient during a maniacal outburst runs away into the jungle and because of his sickness cannot protect himself adequately

Rhodesian Sleeping Sickness

As stated above in the pathology of African sleeping sickness the Rhodesian form shows more visceral and fewer cerebral changes

The symptoms are similar to those of the classic or Gambian type *The* Rhodesian form is more acute The fever is usually higher and there are fewer remissions and intermissions Trypanosomes are numerous in the *peripheral blood The rash is very frequent and of long duration Edema* develops more frequently and is usually extensive

There is little or no enlargement of the lymphatic glands On the other hand disturbances of the cardiovascular apparatus are pronounced Tachycardia is a constant symptom *Later irregularity of the heart action develops*

Convulsions occur very often Mania is frequent

Because of the rapid course of the disease cachexia develops within a relatively shorter time Death occurs within six to twelve months after the onset

Abortive Forms

Persons without history of typical African trypanosomiasis but apparently exhibiting an immunity against the *disease are often found in*

would cause only the feeling of touch evokes delayed pain Often the patient himself complains of unusual pain caused by small impulses

Later the fever decreases but returns after shorter or longer periods of intermission The recurring febrile attacks may be mild or severe The fever may reach various levels but the temperature is always higher in the evening Continuous fever has also been observed

The lymph glands become enlarged The enlargement is most apparent in the cervical glands Winterbottom s sign consists in the observation of enlarged lateral neck glands when the patient turns his back to the examiner The glands are soft but later become very hard They are usually painless but may be tender on palpation When secondary infection is absent they do not suppurate

The spleen is usually enlarged and soft during this period The liver also shows enlargement

The patient often has cramps and paresthesia of different locations and intensities

Persistent tachycardia irritability headaches and insomnia are usual complaints

Manson Bahr (1945) points out the importance of erythemas composed of fugitive patchy annular or irregular rings mostly on the trunk They may be of irregular size and shape and often become huge They fade into the surrounding skin These erythemas are evoked by irritation of the skin by different factors such as heat They are often accompanied by edema

Of great importance are the ocular disturbances Iridocyclitis and chorioiditis are not uncommon Such eye lesions when not diagnosed may develop into serious consequences during treatment with arsenicals

The patient loses weight Anemia develops

This stage of sleeping sickness characterized principally by enlargement of the glands irregular recurring and intermittent fever enlargement of spleen and liver may last for a long time even for years Then either spontaneous cure follows or the cerebral stage begins

Sleeping Sickness Proper

The disease has received its name from the clinical symptoms that accompany this stage also called the cerebral stage " because the psychoneurologic changes induced by the developing brain pathology dominate the picture during it The cerebral stage represents the terminal period of the disease and ends with death It may be acute or chronic It lasts usually three to eight months A more extended duration of sleeping sickness as long as one year has also been recorded

As a rule sleeping sickness proper begins slowly The patient becomes somnolent Desire to sleep during the daytime is usually the first symptom of the onset The intensity of the somnolence gradually increases The patient falls asleep anywhere and in every position If not asleep his actions are lethargic Speech becomes slurred Questions elicit late and retarded answers

Serologic Reactions

Serologic reactions described for the diagnosis of African sleeping sickness are numerous The so called adhesion reaction is sometimes utilized for diagnostic purposes This phenomenon consists of the adhesion of human red blood cells to trypanosomes when trypanosomes are mixed with immune serum complement and red blood cells In the presence of a nonspecific serum no such clumping or adhesions occurs Serologic reactions however have not as yet attained an important place in the diagnosis of sleeping sickness

Clinical Pathology

The blood picture shows secondary anemia The number of white blood cells is within normal limits in the beginning of the disease Leucocytosis appears during the later stages of sleeping sickness There is a relative increase of lymphocytes and of monocytes

Autoagglutinins occur very often causing rouleaux formation of the red blood cells Cold agglutinins have not been found

The blood sugar and the alkali reserve of the blood decrease during the disease The serum is depleted of proteins chiefly of the albumin fraction The albumin globulin ratio is low Nonprotein nitrogen urea and creatinine increase in the terminal stage while the amount of cholesterol usually decreases

During the cerebral stage the spinal fluid contains many cells mostly lymphocytes and plasmocytes The occurrence of plasmocytes in the cerebrospinal fluid is of diagnostic value

As a rule a considerable amount of globulin is present in the spinal fluid The reactions of Pandy Nonne Apelt and Weichbrodt are positive The gold curve shows the paretic type

DIFFERENTIAL DIAGNOSIS

African trypanosomiasis must be differentiated from other generalized infectious diseases such as virus encephalitis malaria leishmaniasis syphilis and leprosy from cerebral and meningeal disorders such as brain tumors general paresis and from pellagra late beriberi and Hodgkin s disease

The differential diagnosis is greatly facilitated by gland puncture if the lymphatic glands are enlarged by the examination of the cerebrospinal fluid and by the search for trypanosomes in the peripheral blood The examination of the bone marrow (sternal puncture) is very helpful

PROGNOSIS

Except for the abortive cases the prognosis is serious in all clinically manifest cases which have not been treated Spontaneous healing is possible but not the rule When the cerebral stage sets in not even intensive treatment can save a great number of the patients

endemic regions The search for abortive infections was intensified when during surveys of the population in infested regions trypanosomes were recovered from the peripheral blood of individuals who did not show classical symptoms Further studies revealed that abortive cases are not rare

There may or may not be an initial rash Low grade fever of irregular character often remittent or intermittent for a few days or weeks is present There is headache and general malaise When one considers that such symptoms may occur in the tropics for a number of reasons it can be easily understood that they may be misinterpreted particularly if means of laboratory examination are inadequate

LABORATORY DIAGNOSIS

It is necessary to keep in mind that the number of parasites in the peripheral blood undergoes considerable fluctuation The parasites are moreover not easily recovered from the cerebrospinal fluid in every case Gland puncture is therefore the method of choice for recovering the parasites if there is enlargement of the lymphatic glands

The Peripheral Blood

Cultivation of the trypanosomes is not as yet so simple that it can be used as a diagnostic method

For animal inoculation guinea pigs are used most often Five or 10 c c of the blood are injected intraperitoneally

Microscopic search for the trypanosomes in the peripheral blood is carried out with the aid of the thick drop method or citrated blood is well centrifuged and the sediment examined

Both unstained and stained preparations are observed For staining the Giemsa method and its modification by Field are recommended *

The Lymph Glands

The lymph glands are punctured after massage using a relatively strong needle and a 10 or 20 c c syringe Smears are prepared and then stained with the Giemsa or Field method While strict asepsis is necessary for this operation no anesthesia is needed

The lateral cervical glands are easily accessible particularly when they are enlarged Massage of the glands during puncture enhances the operation Unstained and stained smears are examined

Cerebrospinal Fluid

The cerebrospinal fluid must be centrifuged in an examination for trypanosomes The sediment can be observed under the microscope injected into guinea pigs or used for cultivation Trypanosomes are often recovered from the fluid gathered through suboccipital puncture and also from sternal puncture material

*See Chapter 63

The best known remedies of African sleeping sickness are tryparsamide and Antrypol

Tryparsamide (Novatoxyl Tryparsone Glyphenarsine) is sodium N phenyl glycine amide p arsonate It is used both in incipient and in cerebral cases It may be injected into the muscles (usually in 10 to 20 per cent solution) The medium dose is 80 mg per kilogram of weight (Manson Bahr) the total dose for one series of injections is 24 Gm Some workers however advocate a total dose of 60 to 100 Gm

According to one schedule three injections are given every week using first 10 c c then 20 c c of a 10 per cent solution These injections are continued for a length of time corresponding to the severity of the disease In advanced cases the following amounts of a 20 per cent solution are injected 3 c c on the first day 6 c c on the fourth and 10 c c on the eighth day then beginning with the twelfth day 12 c c every four days until twenty injections have been given This treatment is repeated after a three month intermission

Another scheme recommends one injection every week first 1 to 1 5 Gm then 2 to 3 Gm according to the weight of the patient A total of fifteen injections is given

Children receive doses up to 80 mg per kilogram body weight for twelve injections

Kellesberger (1943) advocates doses of 45 mg per kilogram of weight a total of 30 to 50 Gm The injections are given once a week If necessary, the series is repeated one to three months later Kellesberger recommends a test injection chiefly in advanced cases Twelve milligrams of the drug per kilogram of weight are injected for this purpose If no untoward reaction is observed the Tryparsamide treatment may be used

Fowler (1945) found that massive doses given by the intravenous drip method are very effective The patients must be hospitalized for this therapy The time of hospitalization is about two weeks Only children and young adults may receive this treatment

Optical neuritis is the most dangerous side effect of the drug The excellent therapeutic results observed in thousands of cases however counterbalance this undesired complication

Antrypol (Belganyl Moranyl Suramin B P Bayer 205 Fourneau 309 Naphuride) is given intravenously in a 10 per cent aqueous solution The total dose is 10 Gm

According to one schedule every fourth day 5 c c, later 10 c c are given until the total dose has been administered

The second scheme calls for the injection of 10 c c on the first third tenth and thirteenth days Then the same dose is repeated once a week In advanced cases doses of 15 c c and even 20 c c have been recommended

Antrypol however is not effective in the cerebral stage of African trypanosomiasis Toxic dermatitis and kidney irritation are observed After a few injections some protein and yellow colored granular casts occur in the urine The appearance of the casts is due to the excretion of the drug through

TREATMENT

The Belgian French and British governments have spent enormous sums for the eradication of sleeping sickness Today when the native populations have learned the advantages of proper medical care the efforts of the colonial agencies are focused on the desire to have every infected person receive a regular course of treatment It has been observed that interrupted or otherwise irregular therapy causes the appearance of drug resistant trypanosomes

The development and nature of drug resistance by trypanosomes is not known It is possible to prove with the aid of microchemical reactions or by the use of fluorescent light that resistant trypanosomes contain less arsenic than the nonresistant forms Eagle and Magnuson (1944) discussed the theories which attempt to explain the origin of drug resistance This coincides with the degree to which arsenic is bound by the trypanosomes Presumably the cell membrane of the organism becomes less permeable to the drug

If a strain of trypanosomes becomes resistant to arsenic it usually does not revert to the arsenic sensitive type with ease When arsenic resistant trypanosomes are picked up by a tsetse fly and transferred to another individual the organisms retain their resistance against arsenic even after passage through the Glossina In other words an arsenic resistant strain may be propagated This phenomenon causes difficulties in the therapy of subsequent cases of infection which cannot be avoided under present conditions Proper treatment is therefore necessary not only for the sake of the patient himself but also for epidemiologic reasons even to a greater extent than in many other communicable diseases

The treatment of African sleeping sickness with arsenic preparations dates back to Ehrlich who dreamed of a *therapia sterilisans magna* possibly through one single injection of an effective drug His first compound Atoxyl however proved to be very toxic The most feared effect of this and other trypanocidal drugs is optic neuritis Ocular lesions in trypanosomiasis were recently studied by Ridley (1945) It seems that diseases of the eye are not rare in sleeping sickness and that numerous drugs aggravate an already present ocular lesion rather than cause a pathology *sui generis* In order to avoid this complication it is essential to examine the eyes periodically with the aid of a slit lamp and an ophthalmoscope during the treatment A very important method of eye examination is to show the patient small objects If even slight impairment of the vision is apparent the administration of the drug must be stopped immediately It must be realized that ocular lesions often develop some time after the treatment has been completed The relatively new aromatic diamidine compounds such as Pentamidine (diamidinodiphenoxy pentane) Stilbamidine (diamidinodistilbene) and Propamidine (diamidinodiphenoxy propane) do not cause ocular lesions but lower the blood pressure As a result of this action many patients suffer collapse The blood pressure however rises again in about one half hour after the injection No fatal incident or permanent damage following the administration of these drugs has been described as yet

General Treatment

Any person who harbors trypanosomes in his body or shows signs of African trypanosomiasis should be isolated in a well screened house The diet must be mixed rich in vitamins Injections of vitamins C and K and of the B complex vitamins are beneficial

When the cerebral stage has already developed, proper nursing care is of utmost importance The patient must be fed Adequate cleanliness must be assured When mental disturbances are present the patient constitutes a real problem in many localities because of the lack of proper psychiatric care and facilities in the rural tropics

Spinal punctures are beneficial No patient should be dismissed before the findings in the cerebrospinal fluid become normal The spinal fluid should be re examined every three to six months for two consecutive years after the clinical cure

Skin lesions and neurologic symptoms are treated according to the established rules of proper medical specialties

No therapy of the optic neuritis is known to date Other ocular lesions are treated in the usual manner

PROPHYLAXIS

Chemoprophylaxis — An injection of 1 Gm Antrypol or Tryparsamide every three to six months is said to protect against African trypanosomiasis

Individual Prophylaxis —The tsetse flies bite during the day Therefore one should travel only during the night in infested areas

The breeding places of the Glossinae must be avoided

Proper mosquito netting is very important

Public Health Measures —Dispersion of the tsetse flies must be prevented Careful control of airplanes coming from areas inhabited by Glossinae has been established and seems to be effective

Removal of the entire population from the endemic area as carried out in Uganda is a good but not always practical measure

Excellent results have been obtained by cleaning the bush and undergrowth at least thirty yards from the water edge, thus destroying the breeding places of the tsetse flies

DDT smoke has been found effective for small foci

Fly traps have been given many trials Not all species of Glossina are however attracted and caught by them

So called fly boys have been used successfully They carry nets and catch tsetse flies

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the urinary system Casts may be found in the urine for about one week after the end of the treatment Neuritis is also ascribed to Antrypol therapy

Diamidine compounds are given in doses of 0 5 to 2 mg per kilogram of body weight in daily injections for thirty days Some workers administer them for a period as long as ninety days Pentamidine is given intravenously Stilbamidine and Propamidine are injected into the muscles or into the veins Propamidine is little used

Stilbamidine has been found to be very effective in the mouse test by Fulton and Yoke (1943) but according to clinical reports other drugs are more effective

Pentamidine was recently tested by van Hoof et al (1944) and was found reliable even for prophylactic use Lourie (1942) Harding (1944) and Saunders et al (1944) agree that this drug must be used only in early cases when the white cell count in the cerebrospinal fluid is still low Harding recommends Pentamidine when fewer than 15 cells per cubic millimeter are present in the spinal fluid while Saunders et al were successful in cases having even as many as 30 cells per cubic millimeter in the cerebrospinal fluid This drug is definitely less toxic than Antrypol or Tryparsamide It must be injected very slowly in order to prevent a sudden drop of the blood pressure which occurs in a number of patients

Among other recently developed drugs Melarsen oxide and 70 A have been found very effective by Weinman and Franz (1945) Recently Melarsen B 2 to 4 mg per kilogram per day in short series has been tried

Combined Treatment

If the treatment with one drug is not effective or when relapses occur another remedy should be chosen Trypanosome strains may be resistant to certain drugs While this resistance is often a result of adaptation to a drug after treatment chiefly arsenicals naturally resistant strains also occur Harding (1945) found that Tryparsamide resistant cases react well to a combined treatment with Tryparsamide and Pentamidine

For combined Antrypol and Tryparsamide treatment Manson Bahr (1945) recommends injections of large doses of Antrypol then twice a week 2 Gm of Tryparsamide or in three to four day intervals 1 5 Gm Antrypol and then after a ten to fourteen day intermission six to eight weekly injections of Tryparsamide 70 mg per kilogram weight for a child 55 mg per kilogram weight for an adolescent and 45 mg per kilogram weight for an adult

Another effective combination is the use of alternate injections of Antrypol and Tryparsamide in three day intervals

Harding (1944 1945) obtained favorable results with concurrent daily injections of 100 mg Pentamidine and 2 Gm Tryparsamide for five consecutive days In more advanced cases however Antrypol and Tryparsamide must be used simultaneously

CHAPTER 10

LEISHMANIASIS, CUTANEOUS, MUCOCUTANEOUS, AND VISCERAL, WITH SPECIAL REFERENCE TO ITS OCCURRENCE IN THE AMERICAS

SAMUEL BARNSLEY PESSÔA

INTRODUCTION

Leishmaniasis is a disease caused by flagellate protozoa of the genus *Leishmania* Ross 1903.

There are three species of the genus Leishmania which parasitize man, all of which are *morphologically identical*.

1. *Leishmania donovani* (Laveran and Mesnil, 1903), which causes visceral leishmaniasis, kala azar, *infantile leishmaniasis of the Mediterranean area, and* the American kala azar or American visceral leishmaniasis.

2. *Leishmania tropica* (Wright, 1903), *which causes cutaneous* leishmaniasis known also as Oriental sore, Biskra button, Baghdad boil, Delhi boil, Lahore sore, Aleppo boil, etc.

3. *Leishmania braziliensis* (Vianna, 1911), which causes leishmaniasis americana or mucocutaneous leishmaniasis, espundia, uta, Baurú ulcer, etc.

HISTORY OF THE DISCOVERY OF THE PARASITES OF LEISHMANIASIS

Leishmanias were first recognized by Leishman (1903). *In the* same year, Donovan described these parasites in a disease called "dum dum fever" or "kala azar." Laveran and Mesnil examined some of Donovan's specimens and proposed the name *Piroplasma donovani*. Ross (1903), however, concluded that this organism was not a sporozoan and created for it the genus *Leishmania*. Nicolle (1908) gave the name *Leishmania infantum* to the parasite which causes kala azar in the Mediterranean area. Wright, in 1903, described a similar organism in a case of Oriental sore in a child from Syria, who had been taken to Boston. He proposed the name *Helcosoma tropicum* for this parasite. Later it was included in the genus *Leishmania*. *The correct name of the parasite which causes Oriental sore is Leishmania tropica* (Wright, 1903). *L. donovani* is identical with *L. infantum*.

American Leishmaniasis

1. **Cutaneous Form.**—The Indian ceramists of the pre-Columbian age in Peru represented on their vases or *huacos* numerous pathologic changes which medical observers and historians later recognized as certain diseases. Tamayo (1909) was the first to recognize *the lesions shown on the* Peruvian huacos as a condition long known as "uta", that is, mucocutaneous leishmaniasis.

In 1895, Greda, in Italy, described the disease in Italians who had returned to their country from São Paulo. In 1908, numerous patients from certain regions *began to report* to the Santa Casa de São Paulo Hospital with a disease at that time known by several names, Baurú ulcer, wild wound, northwest ulcer, etc., but the etiology was not yet known.

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tion, and chiefly by agglutination tests, Marques da Cunha and F Chagas (1937) separated the leishmania which causes *American visceral leishmaniasis* from *L donovani* and *L. infantum* and called it *L. chagasi* Marques da Cunha, however, after further studies, concluded that agglutination is not an adequate *method for separating the various species of the* genus Leishmania For that reason, *L chagasi* has become synonymous with *L donovani*.

MUCOCUTANEOUS LEISHMANIASIS

GEOGRAPHICAL DISTRIBUTION

The presence of mucocutaneous leishmaniasis has been noted throughout most of Latin America from Mexico to the northern part of Argentina The disease shows high incidence *in certain regions*, particularly in parts of Peru and Brazil

In Brazil, the disease is most frequent in São Paulo Silveira (1919) estimated that *there were 15,000 cases in São Paulo*, Pessôa (1941), over 40,000 patients in the endemic region

ETIOLOGIC AGENT

The etiologic agent of mucocutaneous leishmaniasis is *L braziliensis* It has two forms one, the nonflagellate, leishmania form, which is found in the human tissues and in animals susceptible to inoculation with the parasite, the other, the flagellate, leptomonas form *which is found in the digestive tube* of the vector host and in cultures

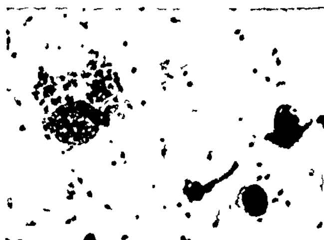


Fig 73 —Smear of material obtained from puncture of a nonulcerative lesion A macrophage containing 62 leishmanias may be observed (Giemsa stain) (After Pessôa and Barretto in I Meeting of Derm Syphil Brazil 1944)

The nonflagellate type might be found also in the invertebrate host just as the flagellate *type might be seen, very rarely, of course,* in the vertebrate host

1 **Forms Observed in the Vertebrate Host**—The leishmania forms appear very often within the cells of the reticuloendothelial system, in smears they generally appear outside the cells due to rupture of the cells while preparing the slides

The typical leishmanias are oval, with one extremity more rounded than the other They measure from 2 to 4 microns by 1 5 or 2 5 microns This form is susceptible to variations The distinguishing *features of the parasite* are the cytoplasm, the nucleus and the kinetoplast

2 **Forms Observed in the Insect Vector.**—When the leishmania forms are ingested by the insect vector, they evolve more or less rapidly to produce the flagellate form

On March 30, 1909, Lindenberg reported discovery of the parasite of Bauru ulcer, this parasite being identical with the agent of Oriental sore This discovery was later confirmed by Carini and Paranhos In 1911, Pedroso and da Silva using N N N medium succeeded in cultivating the leishmania from Bauru ulcer In the same year Splendore demonstrated leishmanias in the lesions of the mucosa In Peru Escomel (1911) found the parasite and identified espundia a disease characterized by slow and progressive ulceration of the bucopharyngeal mucosa, as leishmaniasis

In 1911, Gaspar Vianna considered the differences between the etiologic agents of mucocutaneous leishmaniasis and *L tropica* and proposed the name *Leishmania braziliensis*



Fig ? Peruvian huaco showing lesions attributed to American skin leishmaniasis (After Nelva and Barbará, 1917 First Conference South Amer Soc. Microb & Parasit) Buenos Aires)

2 **Visceral Form.**—The first reference to the possible existence of visceral leishmaniasis in South America was made by Carlos Chagas who while traveling in the valley of the Amazon in 1911 1912 suspected the existence of kala azar in that region Migone (1913), in Paraguay was the first to observe a fatal case of kala azar in the capital of that country Mazza and Arias (1926a) later reported two cases of infantile kala azar in northern Argentina In 1934 Penna reported this infection in 41 sections of liver out of 47 000 specimens Research by a Commission of the Oswaldo Cruz Institute showed the frequency of leishmaniasis in Brazilian territory and clarified the principal points in the etiology, pathogenicity and epidemiology of the disease With the aid of animal inocula

Aragão (1922) found leptomonas in the digestive tube of *Phlebotomus intermedius* and reproduced the ulcer in dogs Pifano (1940), in Venezuela found *Phlebotomus sp* naturally infected by leptomonas in regions of mucocutaneous leishmaniasis

1 In the state of São Paulo there is a notably definite relationship between distribution of the disease and of the *Phlebotomus whitmani*, *Phlebotomus pessoai*, and *Phlebotomus migonei* In regions of endemicity, these three species constitute almost the entire Phlebotomus fauna (Barretto 1943)

There is a two month lapse or period between the maximum incidence of Phlebotomus and new cases of leishmaniasis, this period of two months being within the accepted limits of the incubation period of the disease

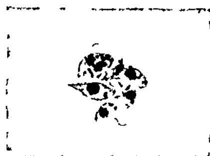


Fig 76—Leptomonas stages in a culture of *Leishmania braziliensis* in NNN medium (Original)

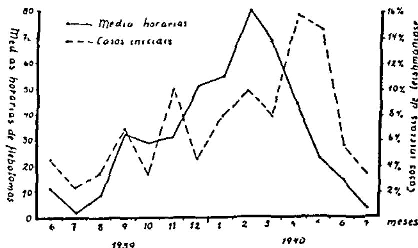


Fig 77—Graph showing the relationship between monthly incidence of Phlebotomus caught with human bait in Pompéia and incidence of early cases of mucocutaneous leishmaniasis (After M P Barretto 1943 In *Observações sôbre a biologia em condições naturais dos flebótomos do Estado de São Paulo* Thesis)

2 Pessôa and Pestana (1940) also found *P migonei* infected Coutinho (1940) observed *leptomonas forms in P pessoai* Finally, Pessôa and Coutinho (1941), examining by dissection and microscopically a total of 9 273 specimens of Phlebotomus found 0 22 per cent to be naturally infected

3 After feeding on individuals or animals infected with *L braziliensis*, the Phlebotomus becomes infected Pessôa and Coutinho (1941) fed *P whitmani*

Culture

Rogers (1904) was the first to cultivate a parasite of the genus Leishmania Nicolle, while studying visceral leishmaniasis in Tunis, showed that *L donovani (L infantum)* can be easily cultivated in the water of condensation of rabbit blood agar, devised by McNeal and Novy for cultivation of *Trypanosoma lewisi* A modified medium has come to be known as N N N medium In 1908, Nicolle successfully cultivated *L tropica* Lindenberg in 1909 and Pedroso and da Silva in 1911 obtained the same results with *L braziliensis*



Fig 74 —*Leishmania braziliensis* Parasites in rosette pattern Smear from an ulcer (Original)

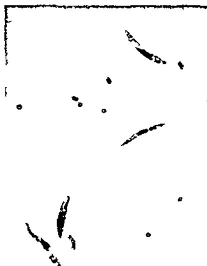


Fig 75 —*Leishmania braziliensis* leptomonas stages found in the pharynx of *Phlebotomus whitmani* naturally infected (Original)

TRANSMISSION

Transmission by Phlebotomus

Long ago the intimate relationship between incidence of Phlebotomus and mucocutaneous leishmaniasis was noticed Several authors, such as Neiva and Penna (1916), Neiva and Barbará (1917) Pirajá de Silva (1918), and Cerqueira (1919), studied the possibility of the transmission of the protozoan by the Phlebotomus

EPIDEMIOLOGY

Latitude—Skin leishmaniasis has been found as far north as 21 degrees in the peninsula of Yucatan and as far south as 30 degrees in Argentina (Bernasconi 1928) as well as in Brazil (Pinto 1942)

Altitude—Altitude is a factor which limits the distribution of the disease for in leishmaniasis as in malaria the vectors become scarcer as the altitude becomes higher Nevertheless Escomel (1929) reported the disease in Peru at an altitude of 2 500 meters above sea level According to Weiss (1943) ' uta (exclusively cutaneous type) has been found in the high regions of the Peruvian Andes at an altitude of 1 200 to 2 800 meters above sea level The dangerous mucocutaneous type espundia is found in the low regions in the forests

Climate—In regions with low temperatures the disease is found along water courses and in the low areas In high temperature areas it is found in the high places where the temperature is suitable to the development of the vector and also of the leishmania in the body of the Phlebotomus

Season—In Sao Paulo Brazil according to Pessôa (1941) the largest numbers of cases appear in autumn (April and June) and they are less numerous in winter and early spring (July and October) Cases occur however throughout the entire year due to the occasional extremely long periods of incubation In Mexico Beltran and Bustamante (1942) noted a high incidence of leishmaniasis from September to December which corresponds to autumn in that part of America

Geography Affected—As opposed to kala azar and Oriental sore American cutaneous leishmaniasis has been shown from the first epidemiologic studies to be a typically sylvan disease

Pessoa (1941) showed that this fact is related to the biology of the transmitting Phlebotomus exclusively sylvan in habits which is found in the woods in great numbers at the time when the weather is hot and after summer rains Since the vector insects do not develop within dwellings or in their immediate vicinity the disease is not found in urban zones even in those cities and villages which are situated in highly endemic regions

Age Sex, and Race—Leishmaniasis attacks without reference to age sex or race Influence of age and sex is connected with the possibility of more or less exposure to the disease The yellow races (Japanese) are not as frequently infected as the white and colored races because as a rule they do not work in the woods Brazilians clear out the forests after which the Japanese settle in districts that have been cleared On certain farms where white black and yellow children live under identical conditions no significant difference has been observed in the incidence of the disease

PATHOGENESIS

General Remarks

The invasion of the human body by *Leishmania braziliensis* usually occurs in the unprotected skin by direct inoculation of the parasite in leptomonas form through the bite of the Phlebotomus After a period of incubation

and obtained 2 17 per cent infections In like manner *P fischeri* were fed, and 0 41 per cent infections obtained

The species which seem to play a predominant role in the dissemination of the disease in São Paulo are the *P whitmani*, *P pessoai*, and *P migonei* The *P fischeri*, with its high incidence in regions of sporadic cases of leishmaniasis, with the possibility of its being experimentally infected, and its marked anthropophilia, seems to be the transmitter of the disease in certain regions

Other Processes of Transmission

1 **Direct Contact**—The possibility of transmission by direct contact has been accepted by several authors

2 **Nonhematophagous Arthropods**—Nonhematophagous arthropods have been incriminated as transmitters of the disease At the present time however, this idea is not accepted because American leishmaniasis is a disease acquired in the forests where flies are not so abundant as in the cities The disease is endemic only in certain definite regions whereas the housefly and other flies can be found everywhere

TABLE X

CLINICAL ASPECTS OF AMERICAN CUTANEOUS LEISHMANIASIS

I Cutaneous	Nonulcerative	(a) Papular (initial)		
		(b) Impetiginous		
		(c) Tuberiform	Sparse	
			In groups	
			In patches	
			Diffuse infiltrative (lupoid) etc	
		(d) Nodular hypodermic		
		(e) Fungoid	Frambesioid	
			Verruciform	
	Ulcerative	(a) Ecthymatiform		
		(b) Ulcerous		
		(c) Fungoid ulcer		
		(d) Nodular ulcer		
II Mucocutaneous	1 With mucous lesion and without apparent cutaneous lesion			
	2 With mucocutaneous lesion	Cutaneous lesion (item I)		
		Mucous lesion	(a) Infiltrative (initial)	
			(b) Ulcerous	
			(c) Fungoid ulcer	
			(d) Fungoid	
III Lymphathic	(a) Adenitis (initial)			
	(b) Adenolymphangitis			

3 **Hematophagous Arthropods, Exclusive of the Phlebotomus**—Several authors have cited hematophagous arthropods other than the phlebotomus as transmitters Da Matta (1910) Flu (1911) Lindsay (1914) etc incriminated ticks, Brumpt and Pedroso (1913), the Tabanidae (horseflies) Phlebotomus however, is probably the only hematophagous arthropod which plays an important role in the transmission of American leishmaniasis

transformed into a large ulcer with infiltration of the margins and slow increase in size indicating that a particular infection has attacked the wound and may determine its later development

CLINICAL ASPECTS

The following classification of the clinical aspects of this disease is taken from the schema of Rabelho (1925) (slightly modified)

Ulcerative Forms—These are the most common They include types indicated in the general picture The ulcerative lesions of cutaneous leishmaniasis show loss of deep substance varying in size frequently attaining or even exceeding 10 cm in diameter These lesions with clear projecting borders have at times high margins intensely infiltrated at times they are irregular moist and violaceous



Fig 78—Mucocutaneous leishmaniasis Ecthymatiform lesion (Original of Aguiar Pupo)

The exudate is serous at times with a purulent secretion stagnating under the brown membrane with which the base is covered and which lies at the level of the surrounding skin If the membrane is detached one can see a bright red base with gross granulations which bleeds easily The infiltrated margins vary greatly in width and height In recent cases the edges are sharp while in older cases the ulcerated surface is gradually lost Often around the larger ulcers smaller ulcers form papular in appearance at first later becoming superficial ulcers

Nonulcerative Forms—The most common nonulcerative forms are the impetiginous and the tuberiform the latter being grouped or scattered They may also be verrucose or frambesioid The last are most commonly encountered The verrucose lesions have a clearer outline and are round with surfaces of irregular wart like form markedly irregular with exudation in the early stages and hard scabs in old dry stages The frambesioid variety is

during which the parasites multiply actively in the form of leishmanias in the histiocytic elements of the skin there appears the initial lesions This is a papule or papular erythema The parasitic corpuscles are found in this lesion

These primary lesions may regress and present an abortive course they may remain stationary, or there may slowly develop skin nodules or in some cases they may further progress to the formation of ulcerative lesions accompanied by neighboring glandular tumefaction These ulcers are at times of a torpid character, at times they go on to natural cicatrization In other cases the lesions progress and at times present a vegetative character with no tendency to spontaneous cure Then by a mechanism as yet not clearly defined by metastasis of the primary lesion the parasites invade the nasobucco pharyngeal mucosa and cause ulcerative or vegetative lesions of a chronic course only rarely with a tendency to spontaneous cure The disease is chronic with a general tendency to invade the mucosae The possibility of a spontaneous cure varies greatly according to geographical areas to the type of lesion and to the part of the skin affected

The disease is also characterized by its irregular course there being no chronology as to the appearance of the various localizations or pathologic manifestations

Period of Incubation

The minimum period of incubation for leishmaniasis of the skin is unknown but according to our observations it is generally short ten to twenty five days Longer periods of incubation have been observed in patients and in experimental animals in some cases as long as ten months to a year

Initial Lesions

After the period of incubation the initial lesions appear These are in the form of papules without any definite identifying characteristics These papules which may or may not be pruritic are accompanied by sensation of heat or pain

The initial stages less frequently assume other characteristics such as erythematous papular lesions of the skin impetiginous lesions small skin nodules etc In the beginning of the disease there is often neighboring lymphadenopathy without apparent involvement of the lymphatic vessels the initial leishmanial lesion is a veritable cutaneous glandular complex Parasitologic examination of the initial lesion shows a great quantity of parasitic corpuscles which are also found in the enlarged lymph nodes The ulcerative process in the initial papule by virtue of necrosis of the outer derma proceeds to the epithelium Detachment occurs with release and scattering of the necrotic material creating an ulcer called "espundia cancrum by Escomel (1911) and espundia cancerum initial cancrum" or cancrum of inoculation by Argentine authors

Another form of beginning ulceration mentioned by several authors is traumatic These cases generally refer to patients with a traumatic lesion which cicatrizes at first only to open later or which may slowly become

In Mexico according to Beltrán and Bustamante (1942), and in Costa Rica according to Rotter and Peña Chavarría (1935) there is a predilection for the ears then the arms the number of ulcers found on the legs and feet being very small Our own experiences have verified the localization in the ears in a percentage of 0 8 to 5 3



Fig 80



Fig 81

Fig 80 —Mucocutaneous leishmaniasis. Ulcerative lesions with fungoid aspect. (Original)
Fig 81 —Mucocutaneous leishmaniasis Papulotuberiform lesions. (Original of Aguiar Pupo)

Mucosal Form—One of the most typical characteristics of American leishmaniasis is the frequency with which the parasites produce lesions in the nasobucco pharyngolaryngeal mucosa This is the difference between cutaneous leishmaniasis and Oriental sore where lesions of the mucosa are exceptional The invasion of the mucosa in American leishmaniasis is a secondary manifestation of the cutaneous lesion Quite often it is difficult to demonstrate lesions in the skin since the disease may have an abortive course without leaving a scar In about 10 per cent of the cases the cutaneous lesions appear simultaneously with lesions of the mucosa but the mechanism should not be considered the same as that in syphilis Although some authors believe

characterized by soft papillomatous lesions resembling those of yaws or bouba This type is called figueira ' in the Amazon (Chagas 1913) and can appear clinically like pé musgoso of pe verrucoso which are caused by various agents *constituting a syndrome This syndrome is found relatively* frequently among our people especially in hospitalized leishmaniasis patients

Lymphatic Form —Lymphangitis and adenitis occur frequently in leishmaniasis The lymphatic vessels are transformed into thick cords of uniform diameter not painful at times with dilatations easily palpable through the skin Such nodules may rupture and become new ulcers This lymphatic form is quite similar to leishmanial lymphangitis and sporotrichosis The lymphatic glands are frequently involved in the initial lesions as well as in the later stages of the disease Marked enlargement of the glands is not very common they are seldom larger than a hazelnut



Fig 79 —Mucocutaneous leishmaniasis Ulcerative lesions (Original)

Number and Localization of the Lesions

There are usually very few lesions one to three there are however some *cases in which* one may find more of these lesions scattered over the body

The lesions are usually found on the exposed parts of the body

In Mexico according to Beltran and Bustamante (1942) and in Costa Rica according to Rotter and Peña Chavarria (193?) there is a predilection for the ears then the arms the number of ulcers found on the legs and feet being very small Our own experiences have verified the localization in the ears in a percentage of 0 8 to 5 3



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Fig 82 —Mucocutaneous leishmaniasis Verrucose papillomatous lesion (Original of Aguiar Pupo)



Fig 83 —Mucocutaneous leishmaniasis Ulcerative lesions and nodules developed in the lymphatic course (Original of Aguiar Pupo)

that infection of the mucosa is due to autoinoculation the majority feel that it is disseminated through the blood stream or lymphatics Villela Pestana and Pessoa (1939) showed that in certain cases localization of the parasites in the mucosa occurs very early Material from currettage of the nasal mucosa in cases with primary skin lesions has revealed parasites in spite of its normal appearance

Initial ulcerations of the mucosa *locate almost always in the nasal* mucosa they begin with hyperemia of the anterior part of the cartilaginous process



Fig 84 —Mucocutaneous leishmaniasis mutilating type Fungoid ulcer of the right forearm and hand destructive lesions of both ears nasal lesion with destruction of the soft parts of the nose and involvement of the upper lip (Original)

After the ulcer has formed it extends deeply into the tissue until there is destruction of the mucosa and invasion of the septal cartilage and of the contralateral mucosa which becomes infiltrated and ulcerated Perforation of the nasal septum is one of the most common consequences of nasal leishmaniasis In many cases the external appearance of the nose remains normal for a relatively long period of time although internally a great deal of damage has been done Destruction is not limited to the membrane of the



Fig 82.—Mucocutaneous leishmaniasis Verrucose papillomatous lesion (Original of Aguiar Pupo)



Fig 83.—Mucocutaneous leishmaniasis Ulcerative lesions and nodules developed in the lymphatic course. (Original of Aguiar Pupo)

septum and to the quadrangular cartilage but may advance and destroy the entire *cartilaginous* frame of the nose, thus causing horrible disfiguration of the patient's face. The ulceration may extend still further and involve both the upper and lower lips, causing dreadful mutilation Generally the bony frame of the nose is preserved

Nasal lesions are persistent, progressive, resistant to therapy, diffuse, by *contiguity* they invade the rhinopharynx, principally the soft palate, the tonsils and their pillars, the posterolateral walls of the pharynx, the larynx, the trachea, and even the tongue and gums In the pharynx, the infiltrative, proliferative process may cause fusion of the uvula, the pillars, the lateral cords, and the posterior wall

Finally, in rare cases, leishmaniasis may localize in the genital or ocular mucosae



Fig 87—Cutaneous lesion in skin leishmaniasis Note marked acanthosis (Original)

Frequency of Localization in the Mucosa: The frequency with which leishmaniasis localizes in the mucosa varies considerably While almost non-existent in certain regions, as in Mexico (peninsula of Yucatan), in other regions, as among us here in Brazil, it is very common

PATHOLOGY

Skin leishmaniasis, from the histopathologic point of view, is a granuloma composed of lymphocytes, plasmocytes, and histiocytic elements, at times in equal numbers, at times with one or another of these types of cells predominating, infiltrating the derma One may notice, in the epithelium, a prolifera-



Fig 85—Mucocutaneous leishmaniasis mutilating type Destruction of soft parts of the nose and involvement of pharynx mouth lips etc (Original)

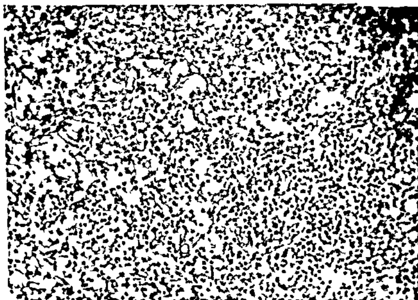


Fig 86—Section of a cutaneous lesion in American skin leishmaniasis. The skin is infiltrated There are seen multiple connective tissue cells and intense lymphocytic infiltration with some plasmocytes and histiocytes. (Original)

by Klotz and Lindenberg (1923) They pointed out the formation of circumscribed nodules of histiocytic cells which characterize the stage of ulceration

There are many leishmanias in the initial papular lesion or dermic nodule —they may be found in extraordinary numbers Leishmanias are also numerous in the margins of recent ulcers which tend to progress rapidly, they usually decrease or even are absent in old and chronic ulcers with a torpid course *As to parasitism cutaneous and mucosal lesions behave in the same way*



Fig 89 —Mucocutaneous leishmaniasis Section of an early lesion of the skin to show the intense parasitism (Original)

NATURAL AND EXPERIMENTAL INFECTION IN ANIMALS

Natural Infection

Pedroso (1923 and 1923a) observed a total of four cases of spontaneous leishmaniasis in the dog Mazza (1926), in Argentina found several dogs with ulcerations in the ears and in the flanks and discovered leishmanias in two In 1927 Mazza reported finding leishmanias in ulcers of a dog and in an ulcer

tive phenomenon—acanthosis. Usually necrosis is produced in the center of the granuloma with loosening of the epithelium and formation of the ulcer. Less frequently the lesion does not ulcerate, constituting the nonulcerative type.

The ulcerative lesions consist of waste substances varying in extent but they extend no deeper than the middle of the derma. *In the smaller lesions* alterations in the margins cause little change in contour of the ulcer. In larger ulcers the epithelial changes are more pronounced and there may be observed marked acanthosis invading the derma in the form of thin epithelial cords close together. Giant cells are sporadic. Well defined tuberculoid structures absent in rapidly progressing recent ulcers can be found in the chronic ulcers

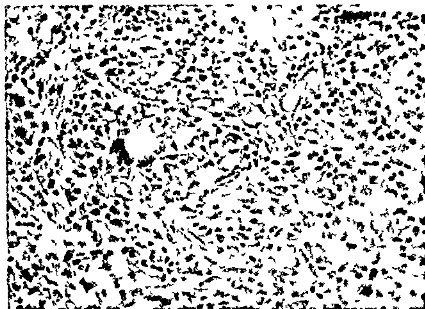


Fig. 66.—Section of mucocutaneous leishmaniasis showing an accumulation of histiocytes and a giant cell. (Original.)

where also well defined tuberculoid nodules can be seen. Eosinophiles are generally not abundant; neutrophiles are found in greater numbers in the vicinity of the ulcer. Fibroblasts, absent in recent ulcers, are found in increasing numbers in the older ulcers with a tendency toward cicatrization.

There is no difference from the histopathologic point of view between the verrucose and papillomatous types. There is always thickening of the skin layers. The stratum spinosum also becomes thickened and there is a formation of horny masses which accumulate in the interpapillary spaces. This proliferation may extend irregularly into the subjacent tissues. The changes involve the derma, intensely infiltrated by histiocytic elements, with elongated and proliferous papillae. Lesions of the mucosae have been thoroughly studied

It is also necessary to differentiate this disease from sporotrichotic lymphangitis this is clinically impossible and is exclusively a laboratory procedure It is also necessary to differentiate it from ecthyma and impetigo In the differential diagnosis between nasal syphilis and leishmaniasis it should be remembered that leishmaniasis affects the cartilaginous parts while syphilis affects the bony structure of the nose Finally leishmaniasis might be confused with Toula and blastomycosis and more rarely with cutaneous and mucosal tuberculosis or with leprosy In all these cases the finding of the etiologic agent solves the problem

LABORATORY DIAGNOSIS

Demonstration of the Parasite

The most important laboratory test is the demonstration of the parasite by direct methods—finding it in the ulcers glands or by culture

Parasites can be demonstrated in material taken from lesions of the skin and the mucosa as well as from glands For this purpose curettage puncture or biopsy may be used As soon as the material is obtained it must be placed in culture media or sectioned for microscopic examination In closed lesions puncture with a large needle is advisable

To find the parasite in the nasal mucosa curettage must be performed after anesthesia with Neotutocaine Material obtained should then be smeared on slides and stained by the Giemsa method

Culture in appropriate media according to some authors increases the possibility of finding the parasite It must be remembered that leishmanias do *not grow in the presence of other microorganisms so that several tubes must* be used to make the culture

Serologic Reactions*

Serologic reactions used for the diagnosis of kala azar do not give satisfactory *results in cutaneous leishmaniasis Complement fixation tests are very* complicated and not very successful because of lack of a good antigen

Intradermal Reaction*

The intradermal reaction also called Montenegro s test is an allergic *reaction It was introduced by Montenegro (1926) and is based on the* work of Wagner (1923) The test was later thoroughly studied by Buss (1929) Gomes (1939) and Pessoa and Pestana (1940)

The antigen is a suspension of leptomonas in phenolized saline solution It is injected intradermally in dosage of 0 1 to 0 2 c c Positive reactions show *the formation of a specific papule* which attains maximum development in forty eight hours remains four or five days and then regresses and disappears in about four days more or less according to its intensity This test gives a high percentage of positive results (about 95 per cent) *It may be negative* in early cases but in such cases parasites can always be found

*See also Chapter 72

in the eye of a horse Mello (1940) at Belém, Pará (Brazil), found numerous leishmanias in material from ulcers in the ear and nose of a cat

Such findings seem to be merely accidental, since examinations have been made of hundreds of cats and dogs, as well as wild animals, without observing any lesions of leishmaniasis Thus dissemination of skin leishmaniasis cannot be attributed to animals

Experimental Infection

The disease has been produced experimentally by inoculation of triturated tissues containing the parasites or by the use of cultures of leishmania in dogs monkeys, and mice [Editor's Note (O F) Hamsters are being used in many laboratories]

More recently, Fuller and Geiman (1942) reported that they had found an animal very susceptible to inoculation with *L braziliensis*—the Texas squirrel, *Citellus tridecemlineatus*

CLINICAL DIAGNOSIS

Cutaneous Form

In general, a diagnosis of cutaneous leishmaniasis is not difficult if the lesions assume the aspect of a typical ulcer Often a glance at the lesion is sufficient to establish its nature If, however, the lesions are verrucose, frambesioid, lymphangitic, etc , they might easily be mistaken for other disease entities, and it is very difficult to make a correct diagnosis In such cases one must make use of laboratory tests The anamnesis aids in clarifying the diagnosis

Mucosal Form

In this type, the anamnesis is very important, because the patients speak of previous lesions of the skin and some of them still carry the evolutionary cutaneous ulcer When these ulcers are no longer present one may find the scars As stated above, in some cases the patients show no skin lesions or subsequent scars The site of the lesion, in the cartilaginous portion of the septum, its granulations and general appearance, all help to make the diagnosis Local edema and hypertrophy, principally of the upper lip, give the patient's face a characteristic appearance which some authors call "facies leishmaniotica " and others "tapir face "

DIFFERENTIAL DIAGNOSIS

The disease must be differentiated from other tropical diseases which are predominant in endemic zones One of the most common of these is tropical ulcer Tropical ulcer localizes in the lower third of the leg, exceptionally in other parts of the body The pain tendency to bleed, abundant suppuration, and odor all are elements which help in the differentiation of the two ulcerative processes

upon lesions of the mucosa to be superior to that of tartar emetic. In this author's experience, however, Fuadin has proved inferior to tartar emetic *for lesions of the mucosa and not superior for lesions of the skin.* One great advantage of Fuadin over tartar emetic is that it can be used by the intramuscular route.

Eparseno (Amino Arseno Phenol)

Eparseno was introduced in the treatment of leishmaniasis by Pupo (1926). It is a glucoside of arsphenamine dioxy diamido arsenobenzol (Manson-Bahr). Each 1 c.c. of Eparseno contains 0.12 Gm. of amino arseno phenol. It is given by injection at two-day intervals. For children there is a proprietary called Infantile Eparseno, *each cubic centimeter of which contains 0.05 Gm. of* the salt, this dosage being used for each 10 kilograms of body weight by intramuscular or intravenous injection.

In general, a series of 10 ampules is given, followed by an interval of ten days, until 40 or 50 ampules, according to the patient's tolerance, have been used. Due to the arsenic content of this drug, toxic phenomena occur at times, such as *diarrhea, intestinal colic, erythrodermia and polyneuritis. In such* cases, treatment should be immediately discontinued and preparations containing vitamin B, as well as strychnine injections, should be used. Injections of Eparseno are the most efficacious means of treating this disease. Lesions of the mucosa refractory to antimony are more rapidly cured with Eparseno. Eparseno is also efficacious in the treatment of cutaneous forms of the disease, cicatrizing the ulcers in a relatively shorter time than tartar emetic. Nevertheless, relapses occur quite often, about as often with Eparseno as with tartar emetic.

Sodium Arsenite

This arsenical compound also was introduced in the treatment of *cutaneous leishmaniasis by Pupo (1935). It is used in doses of 2 to 5 mg. by* intramuscular injection.

It acts efficiently in leishmanial ulcers of the skin. However, relapses are *more common with this treatment than with tartar emetic, and its action on* the mucosa is noticeably inferior to that of Eparseno or tartar emetic.

LOCAL TREATMENT

For the local treatment of lesions, disinfectant substances such as lactic acid are used, or injections of Atabrine, emetine or phosphorated oil are made into the base of the ulcer. Thermocautery and diathermic *fulguration* and coagulation have also been used with more or less success.

Such local treatment is merely adjuvant and should always be used with specific general treatment in the form of injections of antimony or arsenicals.

PROPHYLAXIS

Campaign Against Vector.—We have found that it is virtually impossible to destroy the larval foci of Phlebotomus since we do not know the natural breeding places of the transmitting species.

THERAPY

Tartar Emetic

Tartar emetic was used for the first time in the treatment of cutaneous leishmaniasis by Gaspar Vianna in 1912 It must be used by intravenous injection in a 1 or 2 per cent solution Dosage for adults is 0 10 Gm three times a week the initial dose being 0 06 Gm In children from 6 to 12 years of age a dose of 0 05 Gm is used Injections must be given every other day in a series of twelve to fifteen injections, with an interval of ten to fifteen days Three or four series of treatments are given according to the case and the tolerance of the patient

This drug is not always well tolerated There may be immediate or delayed reactions The immediate bad effects are cough brachial neuralgia nausea and vomiting Delayed reactions are headache various eruptions albuminuria etc These symptoms appear principally after the use of doses larger than 0 10 Gm A very common phenomenon which constitutes one of the greatest inconveniences connected with the use of tartar emetic is rheumatic pain The injections also cause painful reactions in the veins of the arm because this drug causes a certain degree of phlebitis

The treatment must be prolonged even after the period of cicatrization until there is complete disappearance of the nodules or thickenings of the skin Otherwise the lesions reappear within a short time and the therapy already given is useless In the papillomatous and verrucose types which are the more resistant to treatment recurrences are more frequent Recent cutaneous lesions are more prompt to show the beneficial effects of the medication The effect of tartar emetic upon mucosal lesions is the same as upon the skin Recurrences however of lesions of the mucosa are more common

Fuadin (Neoantimosan)

Fuadin was introduced for the treatment of cutaneous leishmaniasis by Mazza and Arias (1931) in Argentina where it is prepared by Bayer and sold commercially in solutions of 6 3 per cent concentration in 1 5 c c and 5 c c ampules The complete series is 30 c c or approximately 1 9 Gm of Fuadin equivalent to 0 30 Gm of antimony

Fuadin is given intramuscularly every other day For adults the first injection should be 1 c c the second 1 5 c c and the third 3 5 c c Following this the 3 5 c c dosage is repeated on alternate days or 5 c c are given every three days Two or three series of eight to ten injections are given with intervals of two or three weeks between the series Dosage for women is two thirds of the dosage for men for children it is 1 c c per each 10 kilograms of weight

Reactions to the use of Fuadin are cough nausea fever, etc In treatment with Fuadin the efficacy of which has been stressed by many authorities, relapses are also common and treatment must be given long after apparent cure of the lesions Mazza and collaborators considered the action of Fuadin

TRANSMISSION

Although *L tropica* can be transmitted by direct contact a fact known for a long time and through the mechanical vehicle of the bite of hematophages among them the *Stomoxys calcitrans*, as shown by Berberian (1938), today it is believed that transmission in nature is effected chiefly through the bite of the Phlebotomus

Adler and Ber (1941) succeeded in demonstrating the transmission of *L tropica* to man (five times out of nine attempts) through the bite of *P papatasii* Other vectors are *P sergenti* and *P caucasicus*

IMMUNITY

According to Thomson (1931) it is believed in Mesopotamia that Oriental sore establishes active immunity and it is customary in routine practice deliberately to inoculate the children in the covered parts of the body to prevent later disfiguration of the face by the naturally acquired disease Nicolle and Noury Bey also state that experimental ulcers confer immunity According to Marzinowski (1928) such immunity has been considered possible for many years Colvilli cited by this author reports that the Jews of Bagdad in order to keep their children from acquiring the disease used to inoculate these children beneath the skin with the serous substance from ulcers

Marzinowski (1928) inoculated himself as well as several of his assistants with exudate from an ulcer All those inoculated showed immunity to new inoculations for seven years following the first inoculation

Adler cited by Thomson (1931) stated that after natural cure of an experimental leishmanial ulcer no new infection followed although the same strain and another biologically different strain were used In the East Marzinowski (1928) Berberian (1939), Gitelson (1928) Lawrow and Dubowskoj (1937) and others have been using as the preferred method of immunization inoculations with living cultures They inoculate with living cultures of *L tropica* which after a period of incubation varying from two to six months cause ulceration which develops into a benign form healing in six to twelve months The last two authors have made more than 500 vaccinations with living cultures They state that no complications have been observed In all cases real immunity is established

PATHOGENICITY

In man the disease is limited to cutaneous tissue and should be designated "cutaneous leishmaniasis" The period of incubation varies from several days to several months The lesion is initiated by a papule which is transformed into an ulcer In cases uncomplicated by bacteria or other microorganisms the lesions show a tendency toward cicatrization and heal at the end of six months or a year leaving a permanent scar Various forms of the disease have been described

Attacks against the adult forms offer more hope of success. Good results are expected from the use of DDT, its action having been proved against several species of arthropods.

Defense Against the Bite of the Phlebotomus.—First there is a need to construct dwellings at a distance from the jungle. According to Takaoka (1928) Phlebotomi do not fly far, so that location of homes more than 100 meters from the woods will prevent invasion by these diptera. Protection of dwellings by netting is not possible in our endemic zones.

Finally, we can recommend the use of mosquito netting, of repellents and the protection of the exposed parts of the body by leggings, gloves, etc. Such methods, while theoretically interesting, are very difficult to apply practically.

Preventive Vaccination.—Preventive vaccination was used by Pessoa and Pestana (1940) and their collaborators of the Commission for the Study of Leishmaniasis. One preventive vaccine is composed of a phenolized suspension of leptomonas, each cubic centimeter of suspension contains 100 to 120 million of these organisms. Three injections with one week interval are made. There is little reaction and the vaccine is well tolerated. Pessoa (1941) demonstrated the efficacy of this vaccination in a highly endemic zone (Table XI).

TABLE XI

RESULTS OF PREVENTIVE VACCINATION AGAINST MUCOCUTANEOUS LEISHMANIASIS (After Pessoa, 1941)

	NUMBER	NUMBER OF PATIENTS WHO DEVELOPED LEISHMANIASIS	PERCENTAGE
Vaccinated	444	12	[illegible]
Not vaccinated	693	108	15.6

CUTANEOUS LEISHMANIASIS

GEOGRAPHICAL DISTRIBUTION

Cutaneous leishmaniasis is endemic in several countries of the Mediterranean area: Italy, Greece, Spain, Morocco, Algeria, Tunis, Tripoli and Egypt. It also is found in some regions of Africa: Abyssinia, Nigeria, French Congo, etc. It is very common in Syria, Palestine, Saudi Arabia, Iraq and other countries of Asia Minor as well as in certain regions of the U.S.S.R. as in the Caucasus and Southern Russia. There are many cases in India and Indochina.

ETIOLOGIC AGENT

The etiologic agent of cutaneous leishmaniasis or Oriental sore is the *Leishmania tropica* (Wright, 1903), the morphology of which is identical with that of *L. braziliensis*.

CULTIVATION

L. tropica was cultivated for the first time by Nicolle in N.N.N. medium. Forms and development are identical with those of *L. braziliensis*, previously described.

Cultivation

Cultures of L donovani may be obtained from the spleen, as Rogers (1904) first demonstrated or from some other organ in which the parasites exist Mayer and Werner (1914) and Wenyon (1914) cultivated them from blood *Shortt and others (1923) succeeded in cultivating them from centrifuged urine*

The behavior and morphology of this species in cultures are the same as those of *L braziliensis*



Fig 91—Section of liver in visceral leishmaniasis Observe the intense parasitism in the endothelial cells (Original)

Habitat

L donovani is found in man in the endothelial cells of the capillaries of the viscera especially of the spleen liver the bone marrow the intestinal mucosa and the mesenteric glands *Leishmanias may* also be found in endothelial cells of the kidney suprarenal capsule lung and the meninges

PATHOGENESIS

The disease is a reticuloendotheliosis due to invasion of the reticular tissues by leishmanias The blocking of the reticuloendothelial system *is con*sidered as the probable cause of the anemia and the tendency toward inflam

DIAGNOSIS

Diagnosis is made by demonstration of the parasite in lesions by smear or culture

TREATMENT

Treatment is similar in general to treatment of American skin leishmaniasis As a rule, however, the disease can be cured with only locally applied drugs Penicillin is very effective

VISCERAL LEISHMANIASIS

GEOGRAPHICAL DISTRIBUTION

The disease is found in some regions of India, as in Calcutta in the Brahmaputra basin in Bengal Assam and the southern part of India it also exists in North China and in Indo China In *Africa* the disease occurs not only in the region of the Mediterranean (Morocco, Algeria Tunis, Tripoli, Egypt), but also farther south in Abyssinia Sudan Kenya, and Nigeria

In Europe it is disseminated throughout southern Russia The Mediterranean area has numerous foci in Yugoslavia Turkey *Greece* southern Italy southern France and Spain Some years ago it was the general belief that in the *European* foci the disease was limited to infancy Recently however, numerous cases have been described in adults

America—The disease has been observed as autochthonous only in South America As has been pointed out the first cases were described in Paraguay and in the Chaco Later numerous cases were observed in Brazil E Chagas and A W Chagas (1938) saw some cases in the Mato Grosso Barros and Rosenfeld (1942) described two cases *in* São Paulo one a patient from Bolivia the other from Ceara In America the disease is always sylvan and sporadic it does not occur in urban zones but only in rural regions and in the jungle

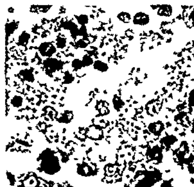


Fig 90—*Leishmania donovani* in spleen puncture (Courtesy of Oscar Felsenfeld)

ETIOLOGIC AGENT

Visceral leishmaniasis is caused by *Leishmania donovani* (Laveran and Mesnil 1903) It has the same morphology as the two species discussed above

The disease is known by a number of names in different regions in India it is known as kala azar (black fever dumdum fever or tropical splenomegaly), in the Mediterranean regions it is known as infantile kala azar or splenic anemia of children, and in South America it is called American visceral leishmaniasis or American kala azar

sive Edema, gastric disturbances and intestinal upsets and small hemorrhages of the nasal and oral mucosa are present Some infections develop acute progressive characters and death may follow at the end of a few weeks or during the first months after initiation of the disease At other times the disease tends from the first stage toward a chronic character, and it may be prolonged for several months or even years

Opinion of authors who have studied this disease is that the lesions in or on the skin constitute the so called "post kala azar dermal leishmaniasis" Such lesions appear some years after the acute state and appear as depigmented areas or in nodule form

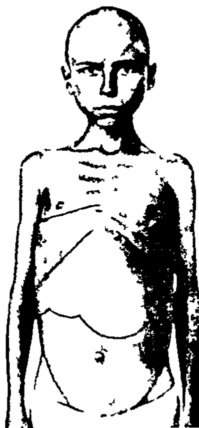


Fig 92—Clinical case of American visceral leishmaniasis (After Chagas E et al Mem Inst Oswaldo Cruz July 1937)

TRANSMISSION

Transmission of *L donovani* occurs through bite of a Phlebotomus which has been infected by biting a diseased man or animal

Transmission has recently been *accomplished (Smith et al* 1940 1941) through the bite of the Phlebotomus The mechanism is a partial or complete blocking of the proventricle and of the esophagus by the leptomonas forms a

matory complications which these patients present The spleen is enormously enlarged the capsule thickened There is a perisplenitis The spleen is congested dark red in color and firm in consistency Microscopically the sinuses of the spleen are dilated with great increase in the number of endothelial cells containing numerous leishmanias A great number of endothelial cells of the vessels are found to be parasitized The liver appears to be equally enlarged Microscopically the cells of the liver are atrophied and degenerated Fatty degeneration is present to a greater or less extent Here as in the spleen the most notable lesion consists in the presence especially in the hepatic sinusoids of numerous endothelial cells densely parasitized by Leishmania Numerous endothelial cells of other vessels become inflamed and contain parasites In advanced cases an increase of fibrous tissue with destruction of parenchyma occurs The bone marrow becomes red and friable and contains numerous macrophages filled with leishmanias as well as neutrophiles containing many of the parasites The lymphatic glands are enlarged and within them parasitized cells can be demonstrated The intestine is often ulcerated the submucosa becoming infiltrated with numerous macrophages filled with leishmanias especially numerous about Peyer s patches

Progressive leucopenia with relative and absolute lymphocytosis is seen in the blood

SYMPTOMATOLOGY

The principal symptoms of kala azar are enlargement of the spleen and often of the liver progressive emaciation anemia and a type of irregular fever Other symptoms may occur such as enlargement of the lymphatic glands pigmentation of the skin and edema The period of incubation varies according to authorities from six weeks to six months After the period of incubation the fever appears as the initial symptom In the first few weeks and sometimes during the first few months the fever reaches high levels (38° to 39° C) and may be continuous or intermittent In the greater number of cases however it is irregular In more advanced stages of the disease the fever becomes very irregular and there may be long periods of apyrexia followed by days and even weeks of pronounced thermal elevation

Emaciation is constantly present Always present in early stages it becomes progressively more alarming at the end of a few months of the disease the patient shows extreme malnutrition As a consequence of the anemia the patient s skin and mucous membranes are very pale In some cases there is change in the color of the skin resulting in characteristic darkening

An increase in volume of the spleen is a very early symptom the organ sometimes attaining enormous proportions reaching to the symphysis pubis Its consistency is very hard so that it is known in leishmanial zones of Brazil by the expression hard as a board (E Chagas) In many regions of South America where the disease has a high incidence splenomegaly caused by malaria is confused with that caused by leishmaniasis For this reason physicians until recently have not always been able to make a clinical diagnosis of leishmaniasis There is hepatomegaly which may be very exten

With *reference to epidemiologic characteristics* of American visceral leishmaniasis it has been proved according to studies made by the F Chagas Commission (1938) that the disease is sporadic and does not assume the *epidemic character observed in Indian kala azar* Its cradle is the forest since it does not occur in urban but in rural districts Although it is primarily a disease of early childhood (1 to 2 years) cases have been found in youths *and adults*

DIAGNOSIS

Clinical—Differential clinical diagnosis should be made from malaria and schistosomiasis If the patient does not improve under quinine treatment malaria may be excluded from consideration Demonstration of the eggs of Schistosoma will confirm a diagnosis of that helminthiasis

Laboratory Methods—These may be direct by examination for the parasites or indirect by serologic reaction Microscopic preparations can be used to demonstrate the parasites in the blood the spleen the bone marrow or the liver These preparations are stained with Giemsa or other methods

The leucopenia may be of great diagnostic value

Blood—Examination of peripheral blood reveals parasites in the leucocytes Since these are difficult to find the blood should be diluted with an oxalate solution and immediately centrifuged in a special container After sedimentation the layer of leucocytes is drawn off with a pipette Histiocytes containing many organisms are easily found A blood culture may be made

Puncture of the Spleen—Puncture of the spleen is the method of choice in the search for leishmanias According to Chagas et al (1938) this method gives the best results in diagnosis It has proved to be quick and efficient in all phases of the disease and practically innocuous To make the puncture a needle 10 cm long and 2 mm in diameter is introduced below the costal margin and at a distance which varies with the type of spleen Generally parasites are found in smears from the splenic pulp in great numbers when the case is recent In the period of the " state of disease " leishmanias are less numerous and for the most part extracellular The pulp may be used to prepare cultures of the parasites

Puncture of the Liver—Resort to puncture of the liver is less frequent than splenic puncture since hepatomegaly occurs later in the disease than does splenomegaly Finding parasites in the liver is more difficult than finding them in the spleen

Bone Marrow Puncture—Usually the sternum is selected when a search for parasites is to be made in the bone marrow They are frequently found In China puncture of the sternum is the method of choice in the diagnosis of the disease in hospitals dispensaries and rural posts It is easier and less dangerous than splenic puncture and may be repeated several times

Indirect Methods—Serologic methods are used quite frequently Some of the principal tests are

Formol Gel Test (Aldehyde Reaction)* This test was used by Gaté and Papacostas (1920) for syphilis but it has been discarded here because of its

*Editor's note (O F) The Chopra Napier test, consisting of the addition of a pentavalent antimony to the blood is little used

fact similar to that which occurs in fleas infected with plague bacilli Hamsters and mice exposed to the bite of the blocked Phlebotomi acquire the disease

In Brazil very few investigations have been made with respect to the possibility of transmission of *L donovani* by our species of Phlebotomus Ferreira Deane and Mangabeira Filho (1939) proved the presence of leptomonas forms in two specimens of *P longipalpis* captured while sucking on a dog which was naturally infected Chagas (1940) succeeded in infecting 75 per cent of the specimens of *P longipalpis* and 75 per cent of *P intermedius* by feeding on a parasitized dog Paraense and A W Chagas (1940) succeeded in transmitting the disease to a hamster by inoculation with a triturate of *P intermedius* which had been experimentally infected

Other vectors are *P argentipes* *P chinensis* *P langeroni* *P major* *P perniciosus* and *P sergenti*

As to the mechanism of transmission it has been shown that *L donovani* develops in the digestive tube of the Phlebotomus in the leptomonas form It migrates to the anterior portion of the pharynx and buccal cavity in six to nine days after the Phlebotomus has sucked on an infected individual it is believed that the Phlebotomus is not infectious until this time

Another possible method of transmission is the ingestion of food or beverages contaminated with *L donovani* This parasite may be found in feces urine nasal secretions, sputum and saliva of patients with kala azar This method of transmission however is of little practical importance

Shortt Craighead Smith and Swaminath (1930) showed the possibility of contact infection They placed healthy hamsters in the same cage with six experimentally infected hamsters Two of the normal animals developed a severe infection with *L donovani*

Natural Infection in Animals

The dog since it is often found naturally infected chiefly in the Mediterranean region and in China is considered a natural reservoir of the disease On the other hand in India human disease is not associated with dogs The natural disease in dogs as in man runs an acute or chronic course with loss of weight fever anemia and enlargement of the spleen and liver The animals may succumb to this parasitosis or to an intercurrent infection but spontaneous cure occurs more often in dogs than in human beings

In Brazil Chagas et al (1938) found visceral leishmaniasis in seven dogs and one cat as well as in other wild animals Dogs with visceral leishmaniasis frequently have cutaneous lesions Chodukin and Sofieff (1930) concluded that these lesions in dogs are a symptom of a generalized infection Richardson (1925) found a horse and de Paolis a sheep naturally infected with leishmania identical with *L donovani* In Russia gerbils are naturally infected

EPIDEMIOLOGY

In the Mediterranean region the infection is most common in children from 1 to 4 years of age while in India the youths are affected although in both regions infection occurs both in adults and in infants As to sex men are more frequently infected than are women

in the treatment of visceral leishmaniasis Chopra (1936) regarded Neostibosan and Urea stibamine as the best of these preparations

Neostibosan (diethylamine p aminophenol stibinate) contains about 40 per cent antimony Each injection of 6 c c contains 0 30 Gm and is given intramuscularly It is the less toxic of the pentavalent antimonials and is especially indicated in the treatment of the disease in children

Aromatic diamidines are being used experimentally in therapeutics They must be used cautiously because of their neurologic action Best results have been obtained with Stilbamidine (4 4'diamido stilbinate)

PROPHYLAXIS

As with *L brasiliensis*, prophylaxis consists of campaigns against the Phlebotomus and of prevention of bites by these diptera Since the infection can be transmitted in feces and urine the possibility of transmission through contaminated food should be taken into consideration An important prophylactic measure is the elimination of dogs which serve as reservoirs of the parasites in endemic regions

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lack of sensitivity Spackman (1921) however noticed that the serum of a patient with kala azar becomes coagulated in a few seconds and not in a few hours as in the test of Gaté and Papacostas

Place 1 c c of the patient s serum free from erythrocytes in a 9 mm. test tube
Add 1 drop of 40% (commercial) formaldehyde
A positive result is indicated by complete coagulation of the serum Coagulation is complete if the serum does not move when the tube is inverted or shaken One hour is allowed for the coagulation process

According to Chagas et al (1938) the test like other serologic tests is not absolutely specific While it is always negative in normal individuals solidification of the serum takes place in other diseases besides kala azar—malaria leprosy bouba and alastrim—although the process takes a long time In American visceral leishmaniasis the reaction is slow in the early stages but increases in rapidity with the degree of infection It is useful in diagnosis of American visceral leishmaniasis in the early stages and also it can be used for evaluating the results of therapy

Brahmachari Test (Reaction of Ray) This consists of the formation of a turbid ring at the point of contact between the serum and distilled water

Allow 2 or 3 c c of distilled water to flow slowly along the walls of a test tube containing 1 c.c. of serum
A turbid ring forms at the point of contact in positive cases the stronger the reaction the more definite the ring

E Chagas et al (1938) used the Brahmachari test in fifty two cases of American visceral leishmaniasis with results similar to those obtained in the formol gel test The reaction is due to increase of globulin principally euglobulin in the serum with corresponding reduction in albumin The reaction is not specific for kala azar but occurs as well in malaria

Other Tests*—Tests using peptonate of iron or Sulfarsenol of Cammino petros etc are little used Complement fixation was especially studied by Moses (1919) and Marques da Cunha and E Dias (1939) They used as antigen cultures of leishmanias washed in physiologic solutions by centrifugation and preserved in acetone for a few days After evaporation of the acetone the leishmanias which remained were triturated and mixed with ethyl alcohol Positive results were obtained with this antigen not only for visceral and cutaneous leishmaniasis but also for Chagas disease This fact has been interpreted as the result of group reaction It is a delicate test and is not readily adaptable as a routine measure

Recently antigens prepared from acid fast organisms are used for complement fixation tests

For intradermal skin tests see Mucocutaneous Leishmaniasis

TREATMENT

In addition to antimonials mentioned above with reference to *L brasiliensis* some pentavalent derivatives of antimony have proved efficacious

*See also Chapter *

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CHAPTER 11

PINTA, MAL DEL PINTO, OR CARATE

FRANCISCO LEÓN BLANCO AND ELVIRA SÁNCHEZ GARCÍA

The first European to use the word "carate" was Gonzalo de Oviedo y Valdez In his work, written between 1505 and 1516, he states that in Castilla del Oro (the region corresponding to present-day Panama and Colombia) the term "carate" was used to designate a certain cutaneous affection which appears to be that which we know today as "pinta," "mal del pinto," and "carate" Thus this disease was *in existence on the American continent before the conquest*, and the word "carate" is of Caribbean origin

"Pinta" is a Spanish word which is used to describe the spotted or mottled appearance of some animals The phrase "mal del pinto" signifies "spotted sickness" or "spotted disease" In Spanish American countries a number of common names are used in speaking of the disease, but there is a growing tendency to use only the words "pinta" or "carate" and the phrase "mal del pinto" to describe the disease and the words "pintous" (pinto) and "caratous" (caratosa) to designate those who are affected with the disease

HISTORY

McClellan (1825) brought this disease to the attention of the Anglo Saxon medical world and called it *pinta* Alibert (1829) made it known under the name *carate* In the past century, the most important contributions to the knowledge of pinta were made by León (1862), Gómez (1879), Ruiz Sandoval (1881), Iryz (1881), and Montoya Florez (1889) *Ruiz Sandoval and Iryz, working simultaneously although independently*, were the first to consider pinta a dermatomycosis A great impetus was given to this theory in later years by Montoya Florez (1898)

Gratz (1913) discovered that salvarsan acted as a specific in carate This impor tant [illegible] and [illegible] the [illegible] lieved that patients with carate were also infected with syphilis or pian (yaws) González Herrejón and Pallares, however, considered the positive serologic test characteristic for mal del pinto *This fact and others served as a basis for his theory that mal del pinto is a* treponematosis different from syphilis and from yaws

Alfonso Armenteros, Grau Triana, and León Blanco found the treponemata in a Cuban case of pinta (1938) León Blanco (1938 1942) demonstrated the constant presence of *treponemata* in Mexican cases of pinta, and the specificity of these organisms

León Blanco described the initial lesion and the early lesions of pinta thus completing the knowledge of the developmental cycle of the affection

Fox (1928 1930), Grau Triana (1937), González Herrejón (1927 1938), Latapi and León Blanco (1940), Pardo Castelló and Ferrer (1942), and Oteiza (1945 1946) also made important contributions to the knowledge of pinta

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CHAPTER 11

PINTA, MAL DEL PINTO, OR CARATE

Francisco León Blanco and Elvira Sánchez García

The first European to use the word "carate" was Gonzalo de Oviedo y Valdez. In his work, written between 1507 and 1516, he states that in Castilla del Oro (the region corresponding to present day Panama and Colombia) the term "carate" was used to designate a certain cutaneous affection which appears to be that which we know today as "pinta," "mal del pinto," and "carate." Thus this disease was in existence on the American continent before the conquest and the word "*carate*" is of *Caribbean origin*.

"Pinta" is a Spanish word which is used to describe the spotted or mottled appearance of some animals. The phrase "mal del pinto" signifies "spotted sickness" or "spotted disease." In Spanish American countries a number of common names are used in speaking of the disease, but there is a growing tendency to use only the words "pinta" or "carate" and the phrase "mal del pinto" to describe the disease and the words "pintous" (pinto) and "caratous" (caratosa) to designate those who are affected with the disease.

HISTORY

McClellan (1825) brought this disease to the attention of the Anglo Saxon medical world and called it *pinta*. Alibert (1829) made it known under the name *carate*. In the past century, the most important contributions to the knowledge of pinta were made by León (1862), Gómez (1870), Ruiz Sandoval (1881), Iryz (1881), and Montoya Florez (1889). Ruiz Sandoval and Iryz, working simultaneously although independently, were the first to consider pinta a dermatomycosis. A great impetus was given to this theory in later years by Montoya Florez (1898).

Gratz (1913) discovered that salvarsan acted as a specific in carate. This important contribution of Gratz passed almost completely unnoticed. Menk (1926) in Colombia and González Herrejón and Pallares (1927) in Mexico, working independently, discovered that the Wassermann reaction is positive in a high percentage of cases with carate. Menk believed that patients with carate were also infected with syphilis or pian (yaws). González Herrejón and Pallares, however, considered the positive serologic test characteristic for mal del pinto. This fact and others served as a basis for his theory that mal del pinto is a treponematosis different from syphilis and from yaws.

Alfonso Armenteros, Grau Triana, and León Blanco found the treponemata in a Cuban case of pinta (1938). León Blanco (1938 1942) demonstrated the constant presence of treponemata in Mexican cases of pinta, and the specificity of these organisms.

León Blanco described the initial lesion and the early lesions of pinta, thus completing the knowledge of the developmental cycle of the affection.

Fox (1928 1930), Grau Triana (1937), González Herrejón (1927 1938), Latapí and León Blanco (1940), Pardo Castelló and Ferrer (1942), and Oteiza (1945 1946) *also made* important contributions to the knowledge of pinta.

ETIOLOGY

Experimental studies by Leon Blanco established the causative agent of pinta as a treponema, he proposed that it be named *Treponema herrejoni*, in honor of the Mexican scientist who had contributed so much to the knowledge of pinta. A few days prior to this proposal Brumpt suggested the name *Treponema carateum*, and according to the rules of priority the latter is the valid name of the species all other names being synonyms.

The characteristics of this treponema (León Blanco) are as follows. When viewed against a dark background it appears as a brilliant cylindrical filament, coiled in a spiral about an imaginary longitudinal axis. The coils of the spiral are tight, regular, and rigid, especially in the center. At times these coils relax and separate to return to their original position just like a steel spring which if pulled apart by both ends, quickly resumes the original position when released.



Fig. 93.—Photomicrograph of *Treponema carateum* (Krajian spirochete stain). Section of skin from autoinoculation with *T. carateum*. (Courtesy of R. I. H. Grauwohl.)

The motility of *T. carateum* is as marked as that of *T. pallidum* of syphilis. It turns rapidly about its longitudinal axis. Its movements of progression are bipolar: it can advance or retreat with equal facility. If it remains stationary, in addition to its spinning or drilling movements, one notices movements of torsion and flection, arching and assuming the shapes of the letters O, P, or S. It also has an unduiant or creeping movement in which the whole body of the treponema participates so that it resembles the movement of a wave of contraction. The organism moves in and out of focus.

After one to six hours, according to the surrounding temperature, the treponema slowly loses its movements until these completely cease. At this time the coils seem to become looser or wider and the body of the parasite then looks like an undulant ribbon in a single plane.

The treponema stains well with Giemsa stain or with aniline dyes. With aniline dyes it is necessary to use a mordant, tannic acid or potassium permanganate. With Giemsa stain the treponema stains a uniform pale rose color. The Krajian and the Fontana Tribondeau methods as used for staining treponemata of syphilis give the organism a black or dark chestnut color.

The methods of Jahnel, Warthin-Starry, and Dieterle also stain the treponemata in tissues very well.*

The organism varies in length between 7 and 22 microns. The average of a large number of measurements is 17 microns. Thickness is approximately 0.2 to 0.3 micron. Depth of the spirals is 0.8 to 1.0 micron. The number of spirals varies according to the length: short specimens have 7, longer ones 15 to 20 spirals.

After several hours of contact, 10 per cent saponin entirely dissolves the treponemata. Bile and 10 per cent sodium taurocholate have the same action. Distilled water causes them to swell.

The treponemata are killed by temperatures of 50° C for fifteen minutes; at 41° C they die within one or more hours.

León Blanco and Oteiza (1945) have recently succeeded in producing pintous scrotal chancres by experimental inoculation of rabbits. Pathogenicity to other animals is not known.

The organisms have not as yet been cultivated.

The distribution of the treponemata in cutaneous lesions in man varies for the initial lesions and pintids and also for lesions of the later phase. In the initial lesions and in the pintids, treponemata are particularly abundant in the epidermis and in the intercellular spaces of the rete mucosum, especially in the acanthotic interpapillary crests as well as in the epithelial portion of the pilosebaceous follicles. In the dermis they are localized especially in the portion occupied by the inflammatory infiltration and they are very abundant near the blood vessels; it is not exceptional to observe them as they traverse the walls of these vessels.

In lesions of the later phase we have never been able to find them in any place other than the rete mucosum and in the epithelial portion of the pilosebaceous follicles.

EPIDEMIOLOGY

Pinta is endemic in rural or suburban areas, stopping at the outskirts of large cities, particularly in countries with a high endemic index. In countries with only sporadic cases, the disease can be found in large urban centers.

In the intertropical regions of the Americas (Mexico, Guatemala, Colombia, Venezuela, Ecuador, Peru, Brazil), the disease is most widely distributed in villages situated in the valleys of large rivers at an altitude which varies from sea level to 2,570 meters (Chillos Valley in Ecuador). In this extensive zone there are places in which the index of infection reaches 50 to 90 per cent (pintogenous zones). There are other localities, situated a short distance from these zones, in which the disease attacks scarcely 1 to 2 per cent of the inhabitants. The cause of this unequal distribution is not clear, but there seems to be one definite factor known about its incidence—*there is no relationship between the disease and geographic conditions.*

*The editor (R. B. H. G.) prefers the Krajian twenty minute stain for spirochetes in smears and tissues (see Chapter 70).

ETIOLOGY

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In Colombia, carate is endemic in all the valleys and especially in the valleys of the great rivers According to Pena Chavarria and Shipley (1925), there are approximately 400,000 cases of carate, although in reality a census of patients has never been carried out This number corresponds to 6 per cent of the total population

Caratogenous zones with the greatest endemic index are found in the valleys of the Magdalena and Cauca rivers, the valleys of Patia and San Juan rivers are of less importance According to the same authors, departments or districts with the highest incidence are Huila, Magdalena, Tolima, Antioquia, Cauca Valley, Bolivar, Antlantico, Caldas, North Santander, South Santander, Boyaca, Cundinamarca, and Nariño

In Venezuela there are about 50 000 cases of carate (Iriarte, 1940) distributed throughout the states of Barinas, Apure, Mérida, Táchira, Trujillo, Lara, Zulia, Portuguesa, Falcon, Bolivar, Yaracuy, Carabobo, and the territories of Amacuro and Amazonas

According to L. A Leon (1940), there are four pintogenous zones in Ecuador, with about 5,700 cases These zones are the valley of the Chillos (pintogenous zone situated at a higher altitude, 2,570 meters above sea level) in the Province of Pichincha, Santa Rosa de Machala, in the Oro Province, Catamayo Valley in the Province of Loja, Archidona, Tena, and Napo, in the Province of Napo Pastaza According to the same author, the disease is highly distributed among the Salasac Indians in the Province of Tungurahua.

There are not even approximate data on the extent of the disease in Peru According to Hercelles (1903), cases of pinta are seen in the District of Suyo, Province of Ayabaca (Department of Piura), in the city of Lima, in Carabaillo, and in Aucayama (Department of Lima), in Palpa, Nazca, Pámpano, and Humay (Department of Ica), in the Majéso Valley of the Province of Castilla, and in the towns of Huancarqui and Uraca (Department of Arequipa) Escomel (1931) has indicated that there are cases in Tambo, Victor, Siguas, Camaná, and in the valley of the Madre de Dios River Weiss (1942) has pointed out the presence of cases in Yarimaguas (Department of Loreto)

In Bolivia Ventemillas (1944) indicated that cases of carate are found in villages situated near the Guapay or Rio Grande river, and Aliaga Suárez, cited by Suárez (1944), has described four pintogenous zones in that country near the Chapare, Rio Grand or Guapay, Madre de Dios, and Heath rivers, to which Suárez adds a fifth, the valley of the Beni River

In Brazil, according to Langeron, there are many cases of carate in the state of Amazonas and in the valleys of the Purus and Juruá rivers In these regions, entire tribes of Indians are affected Silva (1940), Souza Araujo (1940), and Padilha (1944) have identified Brazilian puru puru with pinta

Escobar P (1945) has thoroughly studied and reported cases in Guatemala, these patients coming from the capital, from San Agustin Acasguastlán, from Frajines, Jiquimulilla, and El Molino The extent of the disease in that country is not definitely known, but we assume that the endemic index should be high in zones which border Chiapas (Mexico)

In Honduras the disease was first reported by Lazo Arriaga (1885). In that country it seems to be extensive In British Honduras (Belize) almost all indigenous adults suffer from the disease, according to Browne (1900), according to Cran (1900) not less than 60 per cent of the native population is caratous

In the Republic of San Salvador, Barrientos and his collaborators (1941) reported sporadic cases of pinta

In the United States Lieberthal (1943) and in Argentina Fonso Gandolfo and Rugiero (1942) and Fernández and collaborators (1945) reported cases with cutaneous syndromes similar to those of pinta, with positive or negative serologic reactions But the fact that both of these countries are so far from the zones of endemic pinta and the fact that pintoid cutaneous syndromes caused by syphilis have been described (Lacapare, 1923), plus the fact that it has been demonstrated experimentally that syphilis can produce such syndromes (León Blanco, 1942), inclines us to accept with definite reservations the cases reported in the United states and Argentina as genuine cases of pinta

The index of infection is higher among inhabitants of villages and small towns situated between mountainous zones and the sea than among inhabitants of towns which lie near the coast. In coastal zones rural towns and villages show a higher index of infection than less urbanized areas.

In highly infected villages the disease occurs in family foci. However, intimate contact with pintous patients is not the sole prerequisite for infection, since it is frequently observed that in marriages of one to twenty five years one marital partner may be ill with the disease while the other has remained healthy.

In countries in which pinta is sporadic the infection is not transmitted to those who live with infected individuals.

It has frequently been stated that Indians, Negroes and those of mixed blood (mestizos—offspring of a European and an Indian or Negro) are more susceptible to pinta than the white race. This is not entirely correct, because members of the white race are equally infected when they live under the same conditions as the others. If in Mexico the Indians and mestizos form the largest group of patients with pinta, it is only because they are the dominant population group in the localities where the disease is prevalent. In the Catamayo Valley (Ecuador), where approximately 30 per cent of the population is infected, the disease is found principally among Negroes. There is a somewhat similar situation in Colombia. There is no special susceptibility to pinta on the part of certain races when the mode of life is identical.

Sex has no bearing on the incidence of the disease, at least not in Mexico.

Pinta can occur at any age, but the initial lesion is most often seen in persons between the ages of 5 and 20 years (León Blanco).

GEOGRAPHIC DISTRIBUTION

Pinta or carate has until recently been considered an infection peculiar to countries of the intertropical zones of the Americas. This idea has been challenged since cases thought to be pinta have been found in the United States (Lieberthal 1943) and in Argentina (Fonso Gandolfo and Rugiero 1942, Fernández and collaborators 1945). Pinta may exist in American countries which up to now had been thought to be free from the disease, and also on other continents.

In Cuba, cases of pinta are sporadic and come from the six provinces, in none of which pintogenous zones or foci have been described. It should be emphasized that some of these patients have always lived in the capital of the Republic, and that in a large majority of the cases they have not transmitted the disease to those who live with them. Although the exact number of cases cannot be stated, they have not exceeded 100 to 120.

In Mexico, according to the First Census of Mal del Pinto carried out by the Department of Public Health, there are approximately 2 0 685 cases, a conservative figure if we consider that at the time of the census (1929-1932) the initial lesion and pintids were as yet unknown.

The principal pintogenous zone in Mexico is the vast geographic depression formed by the valley of the Balsas River, including the northwestern part of Oaxaca, Northern Guerrero, a part of Veracruz and almost the whole of Morelos, also the southern part of the states of Mexico, Puebla and Michoacán. Of less importance are zones in the states of Nayarit, Campeche, Tabasco and Chiapas. If we consider the number of inhabitants in Mexico, 1.5 per cent of the total population is attacked by pinta.

Primary Phase

Initial Lesion—It has been possible to follow the initial lesion of pinta throughout its course of development in experimentally infected cases According to latest data in our possession the period of incubation from the time of inoculation to the appearance of the initial lesion varies between seven and sixty days In some cases the lesion appears early, seventy two hours after the inoculation

After the stated period of incubation a rose colored spot punctiform or lenticular appears at the point of inoculation After two or three days this becomes infiltrated assuming an aspect of a rose colored papule oval or hemispherical in shape which stands out in relief 1 to 3 mm from the skin

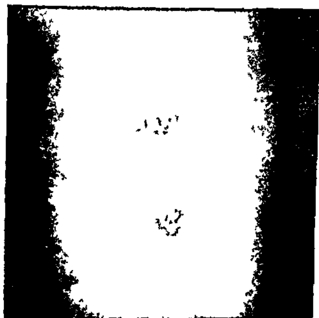


Fig 94 —Experimental double initial lesion approximately 30 days after inoculation Papular phase papules irregular infiltrated covered with scales Inoculum is from one Cuban and one Mexican case Observe identity of development and clinical aspect

or, it may take the form of a slightly infiltrated erythematous small plaque barely raised above the surface of the skin pinkish shiny, and covered slightly with furfuraceous scales The initial papule grows slowly, and invariably, after thirty to fifty days it assumes the appearance of a nummular erythematosquamous plaque clearly outlined against the healthy skin infiltrated to a greater or lesser degree pink and covered with laminar or furfuraceous scales At times the scales in the periphery become partially detached and form a sort of "collar" about the initial lesion In dark skinned individuals it takes on a slate colored hue due to accumulations of pigment in the dermis In very scaly lesions when the stratified scales are carefully removed a shiny surface is seen beneath, sometimes oozing slightly, smooth

Yaws is extensive in Santo Domingo and Haiti It is not definitely known whether this disease can cause pintoid cutaneous syndromes For this reason, there is no assurance that the disease described in Haiti by Audain (1905) under the name "boussarole" is pinta or yaws The same may be said concerning the Dominican "busarola" which is very abundant in Paraje de Malgaren, Province of Seibo

Browne (1901) states that the affection exists along the Gold Coast (Africa) where, on the other hand, yaws is endemic But it is not known whether the affection to which Browne refers (and which the natives according to this author, call "tungere") is pinta or yaws The case described by Bettolo (1940) in Italian East Africa may be vitiligo

Cases described by Madden and Goodman (1900) in Egypt and by Edgar (1901) and by Edgar and Boddaert (1901) in the Malay Peninsula are very atypical and at the time that they were diagnosed, the etiology of pinta was as yet unknown This same statement may be made concerning the case described by Woolley (1904) in the Philippine Islands

SYMPTOMATOLOGY

The experimental work of Leon Blanco and his co workers in the extensive pintogenous zone of the state of Guerrero (Mexico) has demonstrated that pinta begins with an initial lesion, followed after a rather long period of time by scattered cutaneous lesions with clinical characteristics distinctly like those classically known

It seems clear that spread of the treponemata from the initial lesion takes place through the lymphatics or the blood stream The spread of treponemata to neighboring lymph glands takes place in a very early period of the infection However, cutaneous manifestations which indicate clinically the generalization of the infection do not appear until two to four months after the initial lesion, and sometimes not until one or more years later During all this time, the initial lesion is a single cutaneous lesion and serologic reactions remain negative in most cases

From the time of appearance of the first disseminated cutaneous lesions, serologic reactions become positive in a large percentage of the cases The longer the period of development of the disease, the higher the percentage of positive cases From this period, serologic reactions remain constant and strongly positive during the entire course of development of pinta On the other hand, treated cases show negative reactions during the early stages of the disease But after pinta has been developing for years, the serologic tests are unchangeable, even when intensive treatment has been carried out Moreover, the disseminated cutaneous lesions of the early stages of the development of pinta differ clinically from a dermatologic point of view, from the later stages

These facts have led us to conclude that there are two periods in the development of pinta the *primary phase* and the *phase of generalization* In the phase of generalization, two phases may be distinguished, an *early* phase and a *later* phase The study of the symptomatology of pinta, therefore will be divided into three parts The first part will deal with the *initial lesion*, the second, with lesions of the early phase of the period of generalization *(pintids)*, and the third, the lesions of the later phase of the period of generalization *(dyschromic phase)*

colored dots corresponding to small dilated blood vessels filled with blood. Frequently tiny drops of yellowish serous substance, rich in treponemata ooze from the open surface.

Trichophytoid Type.—At times the initial lesion takes on the appearance of perfectly circular erythematosquamous plaques with elevated borders formed by confluent papules. The central portion is of a homogeneous or slightly pigmented pink color and is covered with fine scales. Sometimes, due to partial healing, isolated islands of normal or but slightly pigmented skin are observed within the plaque. These areas are separated by slightly raised pink borders, giving a petaloid appearance to the lesions.



Fig. 96.—Double experimental initial lesion in erythematous squamous phase. Circular discs 3.5 cm. in diameter, infiltrated, with raised border furrowed by deep wrinkles and covered with transparent laminar scales. Inoculum taken from a Cuban case. *Ninety-two days after inoculation.*

Lichenoid Type.—This is characterized by nummular plaques which may be as large as the palm of the hand, irregular in outline, with slightly raised borders. The surface of this plaque presents a shiny cross-hatched appearance due to exaggeration of the natural wrinkles of the skin. The color varies in different subjects, but slate colored tints predominate. Scraping with a curette or spoon detaches adherent scales.

or furrowed by more or less deep wrinkle like folds Around it a hypochromic halo with furfuraceous scales is frequently observed

The surface of the initial lesion continually increases in size although very slowly, by steady excentric growth or by the appearance in the periphery of neighboring papules which fuse with the original plaque as they grow Circular or oval plaques of festooned or circinate contour result from this They retain their erythematosquamous aspect for a long time

In the experimental as well as in the naturally acquired disease the initial lesion develops as the only lesion for a long time It shows different clinical aspects according to the stage at which it is examined In pintogenous

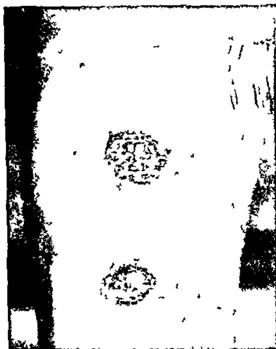


Fig 95—Double experimental lesion 60 days after inoculation Erythematous-squamous phase erythematous squamous nummular lesions covered with laminar scales partially loosened Near both lesions are satellite papules Same patient as shown in Fig 94

zones with a high index of infection there is opportunity to see many patients with initial lesions The lesions in these cases while retaining the fundamental appearance of erythematosquamous plaques present a varied clinical aspect which may be reduced schematically to the following types

Psoriasiform Type—This type is formed by psoriasiform erythematosquamous plaques circular or oval 1 to 5 cm in diameter limited superficially infiltrated and covered with stratified laminar scales grayish white or yellowish white If the scales are carefully removed a pink shiny surface shows underneath slightly moist and seeded with slightly raised papules and with ruby

result in secondary infection which modifies the clinical appearance of th initial lesions of pinta to a slight degree

One or two of the regional glands are almost always enlarged after th initial lesion has been developing for some time In experimental cases th enlarged gland is almost always discrete the diseased gland or glands are har moveable painless about the size of a small bean In the fluid obtaine by puncture treponemata are constantly found upon dark field examinatio

In naturally infected cases we have almost invariably observed one glan enlarged rather markedly this we attribute to superimposed secondary infe tion It is frequent in this type of patient and is due to negligenc



ended to the entire lo er It is formed by one sole slate co ored zones due to loosened Approximately

Early Lesions of the Period of Generalization

Pintids—Although experimental proof is lacking it is evident that dis semination of treponemata from the initial lesion to the various regions of the skin takes place through the blood stream or the lymphatics Localization and multiplication of the treponemata in the skin is manifested clinically at the beginning by a roseola or slightly infiltrated papules

The Large Plaque Type—After a development of some months the initial lesion shows large areas of geographic contours occupying an entire region of the body or at least a major portion of a region The surface is formed by a mixture of zones of normal or slightly atrophied skin pigmented hypochromic or frankly achromic along with other erythematous areas covered with laminar or furfuraceous scales and seeded with smooth or scaly papules The contours of these large plaques are polycyclic and circinate

Transition from one clinical type to another can be verified by observation of patients over a long period of time



Cuban case

The initial lesion is always localized at the site of the portal of entry of the treponema which usually means the uncovered parts of the body Of 257 cases the initial lesion was localized in 163 cases or 63 per cent in the lower third of the leg or in the back of the foot in 67 cases or 26 per cent in the forearms and back of the hand in 15 cases or 5 per cent on the face and neck in 9 cases or 3 per cent on the arms thighs and buttocks and in only one each or 0 5 per cent on the palm of the hand the sole of the foot and on the trunk

The most marked subjective symptom is pruritus In the papular phase the initial lesion is always pruriginous in varying degrees In the erythematosquamous phase pruritus is less marked and almost always intermittent Scratching induced by pruritus produces excoriations which not infrequently

neighboring elements which break out in the area and fuse with the original plaque The first method of growth results in discoid oval or orbicular plaques with a definite outline The second type of growth results in circinate plaques the borders of which are described by *intersecting arcs*

The rose colored spots or papules do not always develop toward the formation of erythematosquamous plaques In an as yet undetermined percentage of cases approximately 30 per cent dyschromic disturbances predominate over inflammation and scales and nummular or larger plaques form These vary in shading from slate blue to steel gray, or they may be hypochromic and decidedly whitish Either type may present a lichenoid appearance

For these erythematosquamous, erythematopigmentary, or erythematochromic plaques Leon Blanco has proposed the name *pintids* This terminology is generally accepted today

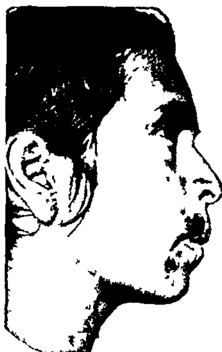


Fig 100—Erythematopigmentary pintids on face and neck The lesions are slate colored masked by erythema Infiltration is very superficial and scales are lacking Naturally acquired disease Mexican case

Sustained study of pintids over a long period of time shows that in the course of months of infiltration erythema and dyschromia are combined quantitatively in variable proportions in the different stages of development of each element This is the cause of the variation in the clinical aspects *In general* erythematosquamous pintids maintain this characteristic during the first year of their development but after this time or even later, the scales become scarce and the erythema attenuates Approximately at the end of the second year the scales usually furfuraceous are barely apparent and erythema very discrete

Between the eighth and tenth days the skin over the rose colored spots or papules up to now but slightly modified shows accentuation of the natural creases and becomes covered with furfuraceous or laminar scales giving the lesion a slightly lichenoid appearance Thenceforward the infiltration increases more or less and the plaque stands out from the surrounding area like a lozenge the scales increase the borders become prominent so that the



Fig 99 Papulo squamous pintids The papules are based on an extensive erythematous plaque which extends over the entire antero internal surface of the thigh Naturally acquired disease *Mexican case*

boundaries of the lesion as related to the surrounding skin can be perfectly seen If the scales are detached at this time a rosy surface smooth or granular may be observed By diascopy the rose color disappears and in its place is seen a whitish surface hypochromic or slightly pigmented After about thirty days the more or less circular elements reach a diameter of approximately 1 to 1 5 cm Growth of the surface takes place either by continuous centrifugal extension or by fusion of a certain number of similar

limitation The margins are generally more active than the center of the lesion In pintids which have been developing over a long period of time or in those which have been treated by topical medication the margins are broken and form intersecting arcs separated by zones of healthy or slightly atrophic skin which gives these pintids a markedly syphiloid aspect

As to their morphology numerous clinical types of pintids may be described psoriasiform gyrate annular petaloid rosette shaped or sheet like etc Because of their similarity to certain syphilodermas and leprous lesions some are described as "syphiloid" or "leproid" pintids etc

The number of pintids varies greatly in different subjects In some cases the outbreak may consist solely of one or two elements in others twenty thirty or a hundred or more may appear In either case they may be localized in the trunk or on the extremities and there is almost always a marked tendency to symmetry

The development of pintids does not occur all at once In the course of the early phase of the period of generalization new elements appear progressively and develop in a manner similar to those which appeared earlier

Pintids as well as the initial lesion may undergo spontaneous cure or at least they might not leave a clinically appreciable cutaneous lesion The disease may pass into a latent phase the sole pathologic manifestation of which is the persistently positive serologic reaction (Wassermann and Kahn) At the end of four or five years or perhaps longer cutaneous lesions begin to reappear localized in the extremities These are in the form of pigmented or achromic spots which may or may not be accompanied by palmoplantar keratoderma We have made these observations (as yet unpublished) in two cases experimentally infected They serve to explain why a certain number of Mexican cases and almost all of the Cuban cases with late manifestations give no history of antecedent initial lesions or pintids possibly the patients have forgotten that they had ever had any such lesions

With the exception of intermittent pruritus and a slight increase in painful sensations pintids present no other subjective symptoms

When the breaking out of pintids is extensive it is almost always accompanied by micropolyadenitis

Cutaneous Manifestations of the Later Phase

In a certain proportion of cases of pinta cutaneous manifestations are permanent from the time of appearance of the initial lesion to the end of life if during this time no adequate treatment has been given In other cases the initial lesion and the pintids may undergo spontaneous cure and the disease may pass into a latent phase after which cutaneous manifestations reappear especially on the skin of the distal portions of the extremities

In the first instance the initial lesion as well as the pintids slowly lose the erythematous and scaly aspect and assume the form of extensive superficial plaques of chronic atrophic dermatitis pigmented or achromic of different shapes and sizes These new elements are not as scaly or congested as the preceding ones but appear as slightly erythematous achromic or pigmented

in the central portion, is more visible in the margins. Now pigmentary changes are the predominant symptom, especially in brunette or dark skinned individuals, and superficial atrophy makes its appearance. In this manner, pintids take on an appearance of plaques that are more or less extensive, of pigmentary or achromic superficial atrophic dermatitis, circinate in contour.

The size of pintids, in general terms, is proportionate to the period of development. Recent pintids measure, on the average, about 1 cm. After a long period of development they may extend over an entire region of the body. Between these two extremes are found all intermediate sizes.



Fig 101.—Palmar pintid of the trichophytoid type. One plaque extends from the cushions of the fingers to two thirds of the anterior surface of the palm. It forms a pink superficies with small slightly achromic or pigmented areas, these last being steel colored, covered with laminar or furfuraceous scales. A similar pintid is on the other hand. Mexican case.

The shape of the pintid is as variable as the size. Up to 3 or 4 cm in diameter, they are more or less circular or oval. The large pintids are polycyclic and assume various shapes. The contour logically follows the shape of the lesion which it circumscribes, but it is usually formed by complete circles or by intersecting arcs. One of the distinctive characteristics is the perfect

face of the trunk They frequently show a slight erythematous tint and are slightly scaly *Ephelis-shaped spots and nummular areas of normally pigmented skin are usually found within the hypochromic surfaces* The margins generally well defined by normal skin describe full intersecting arcs Instead of large surfaces the hypochromic spots may appear as separate spots *the size of the palm of the hand circular or of irregular contour* scattered throughout the skin of the trunk

Generalized clinical forms which are frequent in pintogenous zones where a *high index of infection obtains* give rise to bizarre generalized dyschromias *which gives the patient a harlequin like appearance*



Fig 104 —Leucomelanoderma of the lower extremities Canities of all the hairs Perifollicular and follicular pigmented spots are of brownish or slaty color Mexican case

Because of the generalization of the cutaneous lesions this clinical form *may be considered as a universal dermatosis* the macular process extends to the face, neck trunk and extremities The lesions in each of these regions *present distinct clinical aspects* By summarizing observations of a great number of patients we may state that the lesions in a given region show two or three variations which with slight differences are repeated This being the case we shall for greater clarity *of description* describe that aspect which is generally present in lesions of the face neck trunk and extremities

spots By continuous centrifugal growth and by fusion of these elements with others the dermatosis covers progressively larger and larger areas of the skin

In a given period of time generally after a year of development pinta acquires the characteristics of a universal dermatosis At this point in the development of the disease the most apparent symptoms are achromia and pigmentation But a careful examination shows that these are constantly accompanied by superficial atrophoderma more or less extensive lichenization palmoplantar keratoderma ichthyosiform states of the lower extremities and inflammatory redness of more or less extensive zones of the skin The spotted mixture of all these lesions is a typical and distinctive characteristic of this phase which we have designated as the *late or dyschromic phase* of the period of generalization

When pinta has passed through the latent phase the lesions of the later phase are not so generalized and are circumscribed almost exclusively within the distal portion of the extremities or in certain limited regions of the trunk

After studying a large number of cases we have described from the dermatologic point of view two fundamental clinical forms of the dyschromic phase—one limited to the thorax or the extremities and the other more generalized

In *the form limited to the extremities* the typical clinical picture is symmetrical in both hands and feet Occasionally only the hands are affected or only the feet More rarely only one hand or one foot may be attacked In some cases called *crossed pintos* one hand and the foot on the opposite side of the body show typical lesions

On the dorsal surfaces of the hands and on the lower third of the surface extending along the forearms a superficial pigmented or achromic dermatitis which displays a homogeneous or spotted slate colored appearance is most frequently observed The achromic areas are situated preferentially on the skin which covers the metacarpophalangeal and interphalangeal articulations and the projections formed by the tendons of the extensor muscles of the fingers Extension of achromic areas and of pigmented areas varies widely There are cases in which achromia extends over the entire back of the hand and fingers with only small islets of pigmented skin or on the other hand slaty pigmentation may predominate with only small achromic areas These last extend to the interdigital spaces only when the entire back of the hand has been invaded

On the palmar surfaces of the hands and of the fingers there is generally achromia which can be diffused or limited to certain areas but also along the achromic zones or even within them pigmented slate colored spots of variable shape and size may be observed

In some cases the achromic spots are located on skin which appears to be almost normal perhaps slightly atrophic or scaly without slate colored pigmentation In such cases the skin surrounding the achromic spot frequently shows a slightly more accentuated pigmentation than normal recalling the leucomelanoderma of vitiligo which it greatly resembles But usually the achromia or pigmentation is accompanied by marked atrophy more or less

the other hand very scaly The erythrodermic and pigmented surfaces show intense lichenization or are markedly squamous and the pilosebaceous follicles are the sites of follicular keratosis causing atrophy and the falling out of hair

The hands may be free from or may present all the lesions which we have indicated in localized forms achromia pigmentation hyperkeratosis superficial atrophy etc The lesions have a pellagroid appearance when erythema is intense on the dorsal surfaces of the hands and when it is accompanied by atrophy and slight desquamation



Fig 105.—Leucoderma of the scrotum Dark spots correspond to normally pigmented skin Negro subject. Cuban case

In the lower extremities lesions are similar In the buttocks in the lateral surfaces of the hips and in the thighs hypochromia is often observed in areas of geographic contour which may or may not show many pigmentary carmine or slate colored spots The inner surface of the thighs is frequently spared Reticular leucoderma is often observed in the scrotum

The legs are equally the sites of hypochromia in isolated spots or over a continuous surface or there may be lead colored pigmented erythroderma In some patients the entire leg or the major portion of it is covered with a scaly stocking formed by laminar or furfuraceous scales in the last type

In the case of the *face and neck* it is almost always a question of pigmented erythroderma which extends to the whole face and neck disposed in the form of more or less extensive plaques localized in the cheekbones chin forehead and back of the nose This last formation is usually shaped like a bat In its diffused form pigmentary erythroderma may appear like a mask leaving only a narrow zone 1 or 2 cm wide below the hair line The color varies from intense blue black to lead gray with a livid tint due to erythema In members of the white race or in light skinned mestizos the pigmentation is less apparent and the face neck lobes of the ears and the back of the neck in women show a diffuse reddening Generally there is a distinct edema giving a puffed or bloated appearance to the patient s face as though he were drunk Frequently there is capillary telangiectasis

Pigmentation which at first sight appears homogeneous is formed by confluence of a series of points situated lineally along the dermic crests or around the pilosebaceous follicles

In women whose necks and presternal regions are uncovered the erythroderma takes the exact shape of the uncovered surface

On the trunk the lesions are usually hypochromic or slightly erythematous They take the form of extensive polycyclic plaques with the concavity of their contours directed toward the normal skin The surface of the lesion sometimes shows lenticular spots that resemble freckles or they may be slate colored In a general way the hypochromic areas are symmetrically disposed in the scapular and paravertebral regions separated by a wide zone of normal skin which covers the spinal column On the anterior surface of the thorax in the flanks and on the abdomen the symmetry is less apparent On the shoulders it takes the shape of epaulets

In old cases the hypochromia forms a continuous surface which extends uninterruptedly to the whole shoulder and to the anterior side of the thorax and abdomen At times the skin on the trunk takes on a spotted appearance like the skin of a leopard due to areas of normal and pigmented skin

In the upper and lower extremities the lesions are similar and are situated in homologous regions There is vitiliginous achromia in the elbows and knees in the wrists and ankles in the planes of extension of the forearms and legs There is atrophoderma of the back of the hands and feet In the upper extremities the lesions are symmetrically disposed in the shoulders arms forearms and hands In the shoulders and arms the spots usually hypochromic are distributed in nummular areas separated by healthy skin This produces a mottled effect By growth the spots become confluent resulting in large hypochromic surfaces which extend uninterruptedly from shoulders to hands In some patients the macular process is limited to the surfaces of extension while in others the flexor surfaces are also affected In general achromia is total and vitiliginous in or slightly over or under the elbows Less frequently, the flexion and extension surfaces of arms forearms or of both are the sites of reticular leucomelanoderma or of diffuse leucoderma between which are areas of normal or pigmented skin

In some cases the extensor surfaces of arms or forearms or of both display pigmented erythroderma lead gray or slaty color slightly scaly or on

Dopa oxydase reaction demonstrates that pigmentation coincides with hyperplasia and hypertrophy of melanoblasts although at times a paradoxical state is observed in which there is notable diminution or absence of melanoblasts in a slaty spot with diminution or absence of epidermic melanin This is due to the fact that melanin which has been phagocytized by melanophores may remain stored in them for a long time while melanogenesis is exhausted or remains active only in a few isolated melanoblasts In highly pigmented lesions the dermis is transformed into a reservoir of melanin

The pathologic histology of the initial lesions and pintids is similar Epidermis shows parakeratosis acanthosis intercellular edema which sometimes gives rise to microscopic vesicles and migration of leucocytes through the



Fig 16—Histologic section of initial lesion in the papular phase Parakeratosis enlargement of the interpapillary cones migration of leucocytes across the epidermis Dense infiltration of the papillary structure and of subpapillary portion formed by lymphocytes plasma cells polymorphonuclear neutrophiles and histiocytes Intense edema and marked vascular proliferation

epidermis Cutis shows a dense inflammatory infiltration formed by lymphocytes plasmocytes polymorphonuclear leucocytes and histiocytes In some cases a more or less marked local eosinophilia is observed The inflammatory infiltration is principally perivascular although by confluence diffuse inflammatory infiltration of the entire superficial portion of the cutis may occur Frequently numerous melanophores filled with melanin are observed Exceptionally we see giant cells

The histologic aspect of the lesions of the later phase depends upon the clinical aspect of the lesion taken for biopsy In scaly and lichenoid lesions and in keratodermia there is predominance of parakeratosis hyperkeratosis

the lesion is a dirty gray or silver white color These are situated upon infiltrated cyanotic leucomelanodermic skin in which the creases are exaggerated Pilosebaceous follicles show follicular keratosis

In the feet the lesions are identical to those described in localized clinical forms

Some authors describe pigmentary spots in hairy skin as well as in the mucosa and semimucosa Hair in the diseased area may be normal or atrophic or it may present canities Canities is particularly constant when situated over leucodermic spots

In the nails, punctiform and striated leuconychia has been described but onychogryposis is more frequently observed

In localized as well as in generalized forms but more frequently in the latter the superficial glands show variable enlargement Glands in the axilla and groin may attain the size of a pigeon s egg

Some authors have described aortitis in a great number of patients We have never encountered it Lack of extensive necroscopic investigations prevents affirmation or denial of its presence

Pruritus has been reported by some authors and denied by others In our experience pruritus may be absent or mild or severe continuous or intermittent Scratching frequently produces excoriations with resultant wounds from which oozes serous fluid in which we have found treponemata

PATHOLOGY

All the cutaneous manifestations of pinta are the consequences of localization and multiplication of treponemata in the skin causing chronic superficial dermitis Pigmentation hyperkeratosis lichenization atrophoderma desquamation and all the cutaneous lesions described above are the early or later results of this superficial dermitis

Pintous dyschromia is the result of disturbance of the production and distribution of melanin secondary to a previous inflammation In the hypochromic or achromic spots there is decrease or total absence of cutaneous pigment with decrease or absence of melanoblasts as shown in the dopa oxydase reaction The rosy tint frequently seen in hypochromic and achromic spots is due to inflammatory erythema

Slate blue and lead gray areas and all shades of both are due to an increase in dermic and in smaller proportion epidermic melanin The larger the quantity of pigment in the dermis and the more superficial its localization the darker will be the coloration Weak lead gray color results from lesser quantity of melanin deposited in the dermis and a simultaneous decrease of epidermic melanin Simultaneous increase in epidermic and dermic melanin gives rise to areas with intense blue black color Increase in epidermic melanin without much participation of dermic melanin gives rise to spots of dark red tone the larger the quantity of melanin the darker these spots

The violet color of some areas is due to erythema superimposed on deep pigmentation

DIAGNOSIS

Diagnosis of pinta in the dyschromic phase is not difficult since there is scarcely any dermatosis for which it could be mistaken However, clinical forms localized in the hands and feet, particularly *frequent in countries where* pinta occurs sporadically are indistinguishable from *pintoid syndromes* caused by syphilis and yaws (León Blanco) This is due to the fact that at the pres*ent time there* is no laboratory method which specifically differentiates these three treponematoses

The initial lesions and pintids may be confused only with certain syphilodermas with some epidermomycoses and with clinical forms of cutaneous leprosy or in some cases with pityriasis rosea Laboratory methods permit easy *differentiation of pinta from these last affections* But to differentiate it from syphilis the greatest care must be exercised since all of the diagnostic laboratory methods are the same for pinta as for syphilis In some cases diagnosis can be carried out only after the most minute clinical and epidemiologic studies

The only laboratory methods useful in the diagnosis of pinta are the serologic reactions Kahn Wassermann Mazzini Meinicke etc and the search for treponemata in the cutaneous lesions

In the dyschromic phase serologic tests are positive in practically 100 per cent of the cases Every case which in this phase shows a negative serologic reaction should not be considered as pinta unless treponemata are found in the cutaneous lesions

In the primary period while the initial lesion is the only lesion serologic *reactions are almost constantly negative* *In the early phase* of the period of generalization reactions are positive in 70 per cent of the cases, the percentage increases as the development of the disease progresses

Examination for treponemata in cutaneous lesions and in glands may be carried out by silver impregnation of biopsy material, using the method of Jahnel Warthin Starry Dieterle * or a dark field examination may be made of serous matter obtained by puncture of the glands or by erosion and expression of cutaneous lesions This last method is the most rapid and the easiest *It is essentially as follows* *With a bistoury or curette a very* superficial abrasion is made in the skin of the suspected lesion *Pressure with a pair of* forceps is applied to express a few drops of serous matter from the lesion If the first drops contain many red blood cells they are discarded *until a clear* drop is obtained This drop is mounted on a slide covered with a cover glass and examined under the dark field microscope A smear may be made and stained with Giemsa stain or impregnated by the Krajian or Fontana Tribondeau methods

TREATMENT

In Mexico and Colombia from time immemorial people have used metallic mercury in the form of unguents or vapor for the treatment of pinta as well

*The editor (R B H G) prefers the Krajian method Chapter 70

and acanthosis, and the inflammatory infiltration of the cutis is intense Proliferation and dilatation of blood vessels is marked Elastic fibers are decreased or absent

In atrophic lesions the epidermal layer becomes thinner although at times isolated hyperkeratosis may be observed With disappearance of the inter papillary crests the dermoepidermic line of union is straight or slightly wavy, due to the fact that papillae are erased Elastic fibers are missing in the papillary portion of the dermis On the other hand a condensation of the elastic network may be observed in the deep portion In this type of lesion inflammatory infiltration is absent or at a minimum Frequently the atrophic lesions are achromic at the same time but this is not generally so on the other hand, some pigmentary spots are atrophic at the same time

Treponemata can be demonstrated in all cutaneous lesions by proper methods In the initial lesion and in pintids they are in the epidermis as well as in the dermis In lesions of the later phase we have succeeded in finding them only in the epidermis and in the epithelial portion of the piloseblaceous follicles

The histologic lesion found in the glands adjacent to the initial lesion consists of hyperplasia and hypertrophy of the follicles To this is added inflammatory reaction of the capsule and medulla characterized by presence of plasma cells and lymphocytoid cells Treponemata are encountered constantly

In glands in the later phase a marked inflammatory reaction is observed characterized by infiltration of the lymphoid tissue by plasma cells basophilic cells polymorphonuclear neutrophiles eosinophiles and proliferated fibroblasts This chronic adenitis leads to such marked sclerosis that the lymphoid tissue is reduced to a narrow subcapsular band which like a helmet surrounds the central sclerosed portion of the gland

Generally and constantly in those cases which present extensive dyschromia the affected glands show a bluish or violet color This color is due to the enormous quantity of melanin which accumulates in the glands

MODE OF TRANSMISSION

In 1860 J J Leon stated that pinta was transmitted from human being to human being by the bite of the gegen (gnat*) Since then most authors who have made extended studies of pinta believe that the disease is communicated through a vector possibly a hematophagous arthropod perhaps belonging to the genus Simulium Leon Blanco and Soberón Parra (1941) succeeded in transmitting the disease by using as a vector a fly of the genus Hippelates

The easy transmissibility of pinta from person to person favors the idea of its contagiousness and also the fact that some cutaneous lesions accidentally opened may be potentially infective (Leon Blanco) But the final decision concerning the mode of transmission still rests upon results of research to be carried out in the future

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as bichloride of mercury in the form of lotions potions and pellets Physicians in these countries during the past century recognized the popular tradition and regulated the mercurial medication (León, 1862)

Since Gratz (1913) discovered the curative action of salvarsan in this disease arsphenamine and neoarsphenamine have been used Mercurials and bismuths should be used only if arsenicals cannot be administered Arsenicals cure pinta rapidly in relatively low dosage In pinta there is no reason for the intensive and prolonged treatment such as is used in syphilis

A total dose of 2 50 to 3 50 Gm of neoarsphenamine administered every five days in doses not to exceed 0 60 Gm cures any case of pinta definitively All cutaneous lesions are cured with the exception of leucodermic vitiliginous spots At times deep pigmentations (slaty spots) remain four to six months before they disappear This is due to the fact that reabsorption of melanin takes place slowly

Zozaya and Varela (1943) have used penicillin with as much success in pinta as in syphilis

In the dyschromic phase serologic reactions are irreducible even with the most intensive treatment In the primary period and in the early phase of the period of generalization reactions become negative some months after termination of the treatment

PROGNOSIS

Prognosis in pinta is excellent It does not seem to shorten life and cutaneous lesions are rapidly cured under treatment

With our present status of knowledge of the disease it cannot be stated with certainty that pinta causes visceral lesions such as the aortitis described by some authors It is not known whether the pathologic alterations in cerebrospinal fluid similar to those observed in syphilis and indicated in some cases from Cuba by Pardo Castello are caused by syphilis or by pinta

PROPHYLAXIS

1 The treatment of all patients should be obligatory

2 Contact between normal and diseased individuals should be prevented

3 Hygienic living conditions of inhabitants of pintogenous zones should be improved

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ation with louse borne typhus and in some cases mixed infections of typhus and relapsing fever coexist (Robinson 1942) Apparently there is no reservoir host other than man in the louse borne relapsing fever for this reason the delousing of people and their clothing is an effective means of limiting the spread of the disease

Tick borne relapsing fever occurs usually sporadically Infected ticks transmit the spirochetes of relapsing fever by their bite to man Many species of soft ticks (Ornithodorus) are known to be naturally infected with relapsing fever spirochetes Of the species found in North and South America five species *O hermsi O parkeri, O rudis, O talaje,* and *O turicata* have been proved to be vectors of relapsing fever In Africa Asia and Europe the following species have been proved to transmit relapsing fever *O erraticus O moubata O savignyi O asperus O tartakovski O tholozani* and *O verrucosus*



Fig 107—Thin blood film showing spirochetes of relapsing fever Wright stain (×2700)

Inasmuch as the soft tick remains infected for life and passes the infection through its egg it would seem that Ornithodorus itself is the principal reservoir host of *Bor recurrentis,* although mammals such as monkeys chipmunks prairie dogs rats and squirrels may acquire the infection from ticks and serve as reservoirs for a shorter period

Crab lice *(Phthirus pubis)* and bedbugs *(Cimex lectularius)* apparently play no role in transmitting this disease

PATHOLOGY

Relapsing fever produces no pathognomonic morbid anatomy However the spirochetes may be demonstrated in the spleen brain and other organs

CHAPTER 12

RELAPSING FEVER

ARDZROONY A. PACKCHANIAN

DEFINITION

Relapsing fever is an acute infectious disease characterized by alternating febrile and afebrile periods. The disease is caused by specific spirochetes and transmitted to man by soft ticks (*Ornithodorus*) or by body lice (*Pediculus*).

ETIOLOGY

The etiologic agent of relapsing fever is a spirochete belonging to the genus Borrelia. Many species of this genus have been described as the causative agent of relapsing fever; these so-called species or strains include *Bor. duttoni*, *Bor. hispanica*, *Bor. kochi*, *Bor. novyi*, *Bor. obermeieri*, *Bor. recurrentis*, etc. At the present time it is not definitely known whether these so-called species or races are true separate taxonomic species or whether they merely represent strains or varieties of one or two species. Morphologically, all of the so-called species and strains are identical. Likewise the disease produced by the various "species" are similar clinically. These strains or variants differ from each other principally in their serologic characteristics. It is claimed that in a patient or in an animal any given strain of Borrelia assumes different serologic characteristics during each relapse.

The spirochetes which cause relapsing fever are cylindrical or slightly flattened, with pointed ends, and measure from 8 to 20 microns in length and from 0.2 to 0.3 microns in diameter. Each spirochete has about three to seven large wavy, irregular, inconstant spirals, each spiral having an amplitude of 1.5 microns. These microorganisms are highly motile and divide by transverse fragmentation. Borrelia stain readily with Wright, Giemsa, and other common bacteriologic stains. The spirochete of relapsing fever probably has never been successfully cultured in vitro. Because of their flexibility and small diameter, relapsing fever spirochetes can be passed through a thin-walled Berkefeld filter (Novy and Knapp, 1906).

EPIDEMIOLOGY

Both tick-borne and louse-borne relapsing fevers are widely distributed and found in most parts of the world. The louse-borne disease is found in cold as well as in warmer climates, while tick-borne relapsing fever occurs chiefly in warmer regions.

Louse-borne relapsing fever appears usually in the form of small or large outbreaks or epidemics, although occasionally sporadic cases are encountered. The infection apparently is not transmitted to man by the bite of the infected louse; however, if the louse is crushed and the material is rubbed into abraded skin, as by scratching, infection may take place. So far as is known, the spirochetes of relapsing fever do not pass through the louse egg.

Louse-borne epidemics are frequently associated with poverty, unhygienic conditions, and troop movements. The disease is often found in close associ-

DIAGNOSIS

During the febrile period the motile spirochetes with lashing movements may be demonstrated in a fresh wet preparation of the patient's blood by *dark field* examination preferably with a high power dry objective Stained thin or thick blood smears also are valuable for detection of the microorganisms in the blood The spirochetes of relapsing fever stain readily with Wright Giemsa and other common bacteriologic stains such as gentian violet and basic fuchsin When the central nervous system is involved the spirochetes can be *demonstrated at times in the cerebrospinal fluid*

Inoculation of laboratory rats (Rattus) with the patient's blood is also a valuable method of diagnosis About 5 to 10 c c of the patient's blood taken during the febrile period are placed in a sterile test tube containing a few glass beads and defibrinated by shaking Each of one or two rats is inoculated with 1 or 2 c c of the defibrinated blood The rat's blood should be examined for presence of spirochetes daily from the third to the twelfth day following inoculation as the disease is also a relapsing condition in rats Should it not be possible to inoculate an animal immediately the sample of defibrinated blood may be stored in the refrigerator for a period of several weeks and mice or rats inoculated when desired Defibrinated blood containing Borrelia stored in an icebox for two to three months still retains its power to infect susceptible test animals

Since Borreliae have never been cultured successfully in vitro cultural methods are valueless for diagnosis

Serologic tests are still in the experimental stage and at present are not practical for clinical diagnosis

PROGNOSIS

Relapsing fever is a self limited disease The mortality rate is probably less than 5 per cent but in certain outbreaks the mortality has been estimated at about 20 per cent The majority of cases that terminate fatally apparently are associated with debility malnutrition and other complicating conditions

TREATMENT

Since relapsing fever usually terminates spontaneously evaluation of specific treatment is difficult Although the ideal drug for treatment of relapsing fever remains to be discovered arsenical drugs are most commonly used *and should be given early in the pyrexial period* Detrimental effects have been reported when arsenicals are given immediately preceding the crisis The arsenicals when administered in an afebrile period, seemingly have no effect Some strains of *the spirochetes have a tendency* to become "arsenic fast through inadequate treatment Neoarsphenamine (Novarsenobillon) is given intravenously in a dose of 0 3 to 0 6 Gm for an adult and 0 01 Gm per kilogram of body weight for children One *injection is usually* adequate but injections may be repeated if necessary in two successive days and

Most of the fatal cases are due to complications as heart failure pneumonia or septicemia The spleen is nearly always enlarged and hyperemic and may be the site of microscopic miliary lesions Small capillary hemorrhages are often noted in the various tissues

CLINICAL PICTURE

The incubation period varies from about three to ten days After this fever makes its appearance quite abruptly the temperature rising to 103° to 104° F (39° to 40° C) or more within a few hours The onset may be accompanied by a chill or a chilly sensation Headache and muscular pains are almost constant symptoms and dizziness nausea and vomiting are noted frequently The pulse is increased proportionately to the temperature Slight jaundice is a common finding and in severe cases the icterus may become marked An erythematous eruption may be noted at times Delirium and signs of meningeal irritation may be observed on rare occasions The spleen is often palpable and the liver is usually tender After two to six days of fever the temperature falls to normal by crisis accompanied by profuse sweating

A relapse usually occurs after a three to ten day period which is afebrile and relatively asymptomatic The temperature rises almost as abruptly but seldom goes as high as in the initial attack The relapse as a rule does not last as long and the symptoms in general are not as severe as in the primary paroxysm A second relapse commonly follows an apyrexial period Not infrequently a patient has three or four relapses and in rare cases twelve or thirteen relapses have been reported

LABORATORY FINDINGS

During the febrile period albuminuria is usually present The leucocyte count is elevated to about 10 000 or 20 000 while there is fever The Wassermann reaction is said to be positive in a small percentage of cases

DIFFERENTIAL DIAGNOSIS

There are several febrile illnesses which at the onset must be differentiated from relapsing fever Malaria dengue and typhus would seem to deserve the greatest consideration as the disease progresses Finding *Bor recurrentis* in the patient s blood by direct microscopic examination or by animal inoculation establishes the diagnosis of relapsing fever The presence of Plasmodium in the blood smear indicates malaria A saddleback temperature curve bradycardia and leucopenia suggest dengue fever The similarity of the epidemiology of typhus and relapsing fever and their possible coexistence make their differentiation quite important The onset of typhus is less abrupt and in typhus the fever remains elevated for a longer period Relapsing fever does not give a positive OX 19 Weil Felix reaction although it is reported that the serum of relapsing fever patients agglutinates *Bacillus proteus* OX K (Zarafonetis et al 1946)

CHAPTER 13

LABORATORY DIAGNOSIS OF LEPTOSPIRAL DISEASES

A. Charlotte Ruys

INTRODUCTION

The first leptospiral disease to be recognized as such was Weil's disease. The etiologic agent of this disease was discovered in 1915 almost simultaneously by Inada and Ido in Japan and by Uhlenhuth and Fromme in France in a German military laboratory. The Japanese authors named it *Spirochaeta icterohaemorrhagiae*, the Germans *Spirochaeta icterogenes*. Noguchi (1918) suggested the generic name *Leptospira*. The generally accepted nomenclature at the present time is *Leptospira icterohaemorrhagiae*, priority being given to the Japanese authors. As early as 1916 in Japan Ido, Ito and Wani (1918) isolated another *Leptospira from a patient with seven day fever (nanukayami)* and recognized the organism as related to but not identical with the Leptospira of Weil's disease. Other leptospiras were soon found—*in* Sumatra in patients with relatively mild fevers with clinical pictures different from the typical Weil's disease (Vervoort 1922). During the course of the next twenty five years a number of leptospiras were isolated in Europe, Indonesia, Australia, Africa and India. These differed serologically but the various diseases which they caused resembled each other in their major symptoms although they were quite different epidemiologically.

In this chapter the identification of the leptospiras, the etiologic diagnosis of the disease and the value of the serologic differentiation will be discussed.

The most recent comprehensive surveys on these problems are those of Walch Sorgdrager and Bohlander (1939) and of van *Thiel (1948) to both of* which surveys several references will be made.

MORPHOLOGY

The genus Leptospira belongs *to the family of* Spirochaetaceae and is characterized by a flexible thread like structure consisting of a large number *of regular spiral coils. The amplitude of each coil* is approximately 0.5 micron. The length of the whole Leptospira varies under normal conditions between 8 and 12 microns. Degenerative forms may reach a length of 40 microns. The width is constant and approximately 0.25 micron.

The leptospiras multiply by transverse fission which may be followed under the microscope.

one "stimulation dose" from six to eight days after the second injection Oxophenarsine (Mapharsen) is administered intravenously in doses of 0 04 to 0 06 Gm

Recently, penicillin has been used in the treatment of relapsing fever, with seemingly good results however, the correct evaluation of this therapy and the optimal dosage will not be known until more cases are observed

In cases that fail to respond to arsenicals sodium or potassium bismuth tartrate given intramuscularly has been reported to be of value

Inasmuch as the spirochetes of relapsing fever are found in the brain and cerebrospinal fluid in rare cases and since neoarsphenamine and penicillin do not reach the cerebrospinal fluid in effective quantities relapses may be due to the persistence of the spirochetes in the central nervous system The use of the pentavalent arsenicals (as tryparsamide or Aldersone) may be of value but have not been given an adequate trial as yet

Symptomatic treatment and good nursing care assume great importance in the more severe cases

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A strongly active Giemsa solution in tap water should be applied on the dried smear for 30 minutes at 37° C. Then the stain is renewed by a fresh Giemsa solution which is again applied for 30 minutes at 37° C. Victoria blue may also give good results. Great care must be taken to use clean slides and to wash away the stain very carefully by allowing the water to drip on the stain covered glass and rinsing the precipitate with the water. In well stained smears the color of the leptospiras is violet and the separate coils can be seen distinctly.

Leptospiras can be demonstrated in tissues by the Levaditi method.* Often they do not show the elementary spiral coils but they can be easily recognized.

At times a division into a number of micro leptospiras may be seen in films of old cultures. Gastinel and Mollinedo (1942) described in leptospiras granules with coiled filaments. They are invisible in the dark field; their nature is obscure.

FILTRABILITY

Leptospiras are able to pass through the pores of various filters. Their great flexibility, their extreme thinness and their actively boring movements permit them to pass through the pores.

NUTRITIONAL REQUIREMENTS

Growth requirements of leptospiras are not very complicated. They can be grown in a simple buffered peptone solution:

Peptone Wittet	0.1 per cent
Phosphate buffer pH 7.2	10 per cent
Distilled water	1 liter

Growth in this rather poor medium is, however, not very copious and often it is not even visible at all, so that for experimental and diagnostic work it is necessary to add some enrichment. Rabbit serum is widely used for this purpose, sometimes in combination with hemoglobin. One of the simplest media is that of Vervoort (1922), wherein growth is luxurious. Sometimes, however, the tap water is not suitable for cultivation.

Vervoort Medium

(Modified by Wolff and Schüffner)

Peptone Wittet	1 Gm
Ringer's solution	200 c.c.
Sørensen's phosphate buffer (pH 7.2)	100 c.c.
Tap water	1000 c.c.

Boil until the phosphates have been precipitated and filter after cooling. Distribute into small tubes. Sterilize at 100° C. The pH is 6.9 to 7.0.

Add 10 per cent sterile rabbit serum and inactivate at 56° C. for 30 minutes. Some rabbit sera agglutinate the leptospiras and cannot be used in the media, so that each rabbit serum must be previously tested.

*The editor (R. B. H. G.) refers the Levaditi method described in Chapter 0.
†Editor's note (O. F.): In America Difco or BBL peptones are used.

It is impossible to examine living leptospiras with the ordinary micro scope because the index of refraction is nearly the same as that of the sur rounding media (plasma urine culture fluid) Only with a dark field con denser can they be easily recognized

With a not too high magnification they look like strings of very closely packed small beads They have hooked ends and a rather rigid middle part and move only slowly through the field with rapid rotation on the longi tudinal axis When the medium is viscid they seem to have some traction and acquire some speed Then also the middle part may show its great flexi bility the movement becoming like that of a snake Sometimes the ends ex hibit a whipping motion

Great care must be taken not to mistake so called pseudoleptospiras for real ones Often thread like fibrin structures are expelled from the blood corpuscles in blood specimens These may show movements caused by cur rents in the liquid perhaps also by Brownian movement and may easily be mistaken for leptospiras



Fig 108 —Leptospiras stained with Giemsa solution after fixation with osmic acid vapor (×1500)

STAINING

Leptospiras cannot be easily stained They do not stain with simple dyes like gentian violet as the Borreliae do Gram s method is of no use for this purpose Good results can be obtained by staining with Giemsa solution The oldest method is that of Zuelzer who fixed the films with vapors of osmic acid and stained with Giemsa solution However Schuffner (1934) showed that the easiest method is to stain the films after drying without preliminary fixation With the usual fixatives the primary coils become invisible *

*The editor R. B H G prefers the Krajian method described in Chapter 70

to keep the cultures alive Incubation is mostly between 28° and 32° C To obtain rich cultures it is necessary to seed with large amounts of material For subculturing nearly one half of a cubic centimeter of the old culture is transplanted into the fresh medium

VIABILITY AND RESISTANCE

In cultures leptospiras may show a remarkable viability Cultures in Vervoort's medium kept *in the dark at room temperature without subculturing* sometimes remain alive for years Dinger (1932) demonstrated that in the *semisolid medium of Noguchi* a thick layer of leptospiras grows 10 to 12 mm below the surface and these organisms may remain fully virulent for years

Leptospiras are very sensitive to acid reactions They are killed very quickly in acid urine *To isolate them from urine it is advisable to alkalinize* the urine by keeping the patient on appropriate diet for some days before collecting the specimen They are not very sensitive to salts They may remain alive in sea water for several hours but they disappear more quickly from salt and brackish water than from fresh water (Ruys and Schüffner 1934)

They are killed at 50° to 55° C in 30 minutes They tolerate low temperatures well (Zuelzer, 1925) They can be kept alive in tissues for several months when frozen at -20° C In culture fluid at this temperature however they survive no more than five days They cannot be preserved by lyophilization (Stavitsky, 1945)

They have little resistance against the various disinfectants Bile kills them quickly They are not susceptible to sulfonamides Of the antibiotics penicillin is active it has been used successfully in animal experiments (Larson and Griffitts 1945 Borg Petersen and Rotwitt Schmidt 1945) Good results have been reported in a few patients

ANTIGENIC STRUCTURE

Soon after the discovery of leptospiras as the etiologic agent of various infections the question arose as to whether those strains which differ serologically are independent species or whether they are mere variants of the same species *This problem has not been solved to date and both theories* have their adherents The first strains recognized as differing from the classic Weil strains were *L hebdomadis, L akiyami* A in Japan, and *L pyrogenes* in Sumatra all of which cause an acute febrile disease but mostly without jaundice and with a much lower death rate than Weil s disease

When still more serolog cally *different stra ns had been isolated a more elaborate study* of the antigen c structure became necessary, especially since the various strains cause almost the same clinical *picture in man the d fferences be ng unimportant* and only in degree In addition the virulence for animals is not a reliable means of differentiation e ther

Antisera *from patients or sera prepared* by injection of cultures into rabbits agglutinate cultures of leptospiras often in a h gh titer

Because *of the very faint visib lity of the* leptospiras in ord nary light the agglutination is poorly visible macroscopically Pot (1936) reported that concentrated formal n killed

Another suitable medium is that of Korthof (1932), which is a slight modification of Vervoort's medium

Korthof Medium

Peptone Witte*	400 mg
NaCl	700 mg
$NaHCO_3$	10 mg
KCl	20 mg
$CaCl_2$	20 mg
KH_2PO_4	90 mg
$Na_2HPO_4 \cdot 2H_2O$	480 mg
Distilled water	500 c c

Heat the mixture for 20 minutes at 100° C cool and filter Sterilize at 100° C Then add 8 per cent of sterile fresh rabbit serum Tube the mixture and inactivate for one hour at 56° C

Noguchi (1918) prepared a semisolid medium in which growth is excellent but which is not suitable for agglutination experiments

Noguchi Medium

Rabbit serum	1 5 parts
Ringer s solution	4 5 parts
2% agar	1 0 part
Paraffin oil to cover the surface	

Noguchi used this medium also in combination with a fluid medium consisting of 1 5 parts of rabbit serum and 4 5 parts of Ringer s solution poured over the solid medium the whole covered with paraffin oil A drop of rabbit hemoglobin—1 part of defibrinated rabbit blood + 3 parts of distilled water—may be added to improve the results

Savino and Renella (1944) prepared a medium with several enrichment fluids

Savino Medium

KH_2PO_4	2 Gm
NaCl	3 Gm
MgSO	0 05 Gm
$CaCl_2$	0 01 Gm
Distilled water	1000 c c

Add as activator 0 1 per cent of yeast extract 0 5 per cent of caseine hydrolysate and 0 005 per cent of hematin

Adjust the reaction to pH 1 with HCl

Sterilize for 15 minutes at 115° C

Add 10 per cent sheep serum sterilized by filtration

Other media have been advocated—egg agar chorioallantoic membrane etc —but these have no advantages as compared with those described above which are simple to prepare and easy to handle the fluid media can be used in agglutination experiments

Leptospiras must be cultivated under aerobic conditions The optimum temperature for rapid growth is 37° C but lower temperatures are necessary

*Editor s note (O F) In America Difco or BBL peptones are used

is diluted with the *remaining culture fluid*, and it *might become too greatly diluted* if more strains were used. We have no absolutely monovalent sera such as we use in our bacteriologic serologic work.

Strains of the same species remove antibodies from a serum, strains of a related one only those belonging to the strain itself. The clear cut results obtained with this method allow of an exact identification. Several species are now recognized as serologic and biologic entities in which there is correlation with a distinct *epidemiologic behavior*.

However, strains considered to be of the same species may show minor serologic differences. Borg Petersen (1938), whose work was confirmed by Gispen and Schuffner (1939), demonstrated that the classical Weil strains fall into two groups, one complete with the antigens A and B, the other incomplete with only A. Both behave alike pathologically and epidemiologically, so that they may be considered as two biotypes of the same species. Probably the same relation exists between *rachmat*, incomplete, and *akiyami A*, complete biotype. Van Riel found the same relation between an Indonesian strain (Benjamin) and an African strain (Mukingilwa), neither of which has been fully tested with all other sera. According to van Riel, *L. canicola* also has the two types mentioned here. Table XII is a list of strains examined with agglutinin absorption tests.

TABLE XII

MICROORGANISM	PATHOGENIC FOR MAN	DISEASE	PRINCIPAL HOST	OTHER ANIMALS FOUND INFECTED
L. icterohaemorrhagiae (complete and incomplete biotype)	+	Weil's disease	R. norv. norvegicus	R. ratt. rattus, R. ratt. alexandrinus, dog, fox, horse, pig, sheep, Arvicola terrestris
L. canicola	+	Canicola fever	Dog	
L. grippotyphosa (*L. andaman B*)	+	Mud fever, harvest fever	M. arv. arvalis	Cl. glareolus, A. sylvaticus
L. bataviae (*L. mitis*, *L. oryzeti*)	+	Indonesian, Weil's disease, rice field fever	R. norv. norvegicus, Micromys minutus soricinus	R. ratt. brevicaudatus, cat, dog, R. ratt. diardi, A. sylvaticus
L. sarkoebing	+	?	A. sylvaticus, A. flavicollis	–
L. sejrø	+	Sejrø fever	Mus spicilegus, A. sylvaticus	–
L. pomona (*L. australis C*)	+	Swineherd's disease, leptospirosis, australis C	Pigs	Dog, R. norv. norvegicus
L. australis A (*L. ballico*)	+	Cane fever	R. ratt. culmorum	Dog, R. norv. norvegicus, R. ratt. rattus
L. hebdomadis	+	Seven day fever, nanukayami	M. montebelloi	*Dog*
L. pyrogenes (*L. salinem*, *L. australis B*)*	+	Spirochaetosis febrilis	?	R. ratt. brevicaudatus
L. autumnalis (*L. rachmat* incomplete, *L. akiyami A* complete)	+	Autumnalis fever, hasami, akiyami	R. ratt. brevicaudatus, A. speciosus	M. montebelloi
L. ballum	+	?	Mus musculus (white variety)	Mus spicilegus
L. javanica	?	?	R. ratt. brevicaudatus, R. ratt. concolor	R. norv. norvegicus, *R. ratt.* diardi

A, Apodemus. R, Rattus. M, Microtus. Cl, Clethrionomys.

*In agglutination tests these are the same; in absorption tests there are small differences.

cultures may show agglutination visible to the naked eye, but unfortunately with these antigens the titers are lower and a much greater quantity of cultures is needed

This method and others based on the same principle have found only few followers, so that the serologic tests must be controlled by the dark field examination Serum dilutions made with a buffer solution are mixed with equal quantities of a rich culture and kept at room temperature After two hours, the results can be read provisionally, but the titer is not determined until the next day

In the lower dilutions of a strongly active serum, agglutination is clearly visible, in the higher dilutions, lysis complicates the picture The conglomerates of agglutinated leptospiras begin to show signs of lysis, until, at the end, only shapeless balls can be found, and finally nothing is seen except a few freely floating single leptospiras The titer end point is the last dilution of the serum which shows some difference in number with the control

Attention must be called to the fact that sometimes "nests" of leptospiras grow in rich cultures These may resemble agglutinated leptospiras In the "nests," however, each leptospira is entire and actively moving, in agglutinated conglomerates, the leptospiras have a damaged appearance and the movements finally cease

To avoid the danger of working with living leptospiras and to be able to have a stock of antigen ready at hand, some laboratories use formalin killed cultures It is necessary to use chemically pure formalin and no more than 0 5 per cent Impurities may cause nonspecific acid agglutination (Zuelzer, 1932) When dead cultures are used however, the lysis is absent and agglutination becomes manifest in much higher dilutions than with living cultures, where this phenomenon has been obscured by the lysis The titer of the sera tested with killed antigens is on the whole somewhat lower than when the titer of lysis is determined with living ones (Walch Sorgdrager Schuffner, Bohlander, 1938) The results with these antigens are less specific than with living organisms The formalin antigens can be kept for a limited time only because clumping begins sooner or later, probably caused by formic acid originating from the formalin under the influence of light

Complement fixation tests have also been used in serologic work but they are less specific and have practically been abandoned To determine the antigenic structure of a strain, monovalent rabbit sera are used, which should have a titer of not less than 10,000 They agglutinate and lyse strains of the same species to the same titer or sometimes less, the lowest being one tenth of the titer

Other species may show a strong co reaction, but they never reach more than one third of the titer (Walch Sorgdrager 1938, Walch Sorgdrager and Bohlander, 1939)

Some species are serologically closely related (*L canicola L icterohaemorrhagiae*), others are independent (*L bataviae*) For an exact diagnosis, however, agglutinin absorption tests are necessary, especially in those cases where co reactions are strong The absorption test first described by Ruys and Schuffner (1934) and improved by Schuffner and Bolander (1939) is made as follows

Agglutinin Absorption Test

Use a well grown culture in Vervoort's medium, killed with 0 5 per cent formalin Centrifuge 100 c c of this culture for 20 minutes at 10,000 r p m

Pipette off the supernatant fluid

Mix the remaining 0 45 c c of concentrated culture with 0 05 c c of the serum diluted to a titer of 1 3,000

The antibodies are fixed within 4 hours, but the mixture can be left overnight at room temperature

Centrifuge at 10,000 r p m for 5 minutes, and use the supernatant fluid for agglutination tests Van Riel (1946) prefers to perform the absorption with living cultures

It is difficult to absorb a serum with many strains because a leptospira culture cannot be entirely deposited at the bottom of a tube, and some fluid remains in the tube The serum

demonstrate the leptospiras The culture is the most reliable method but it often gives positive results only after quite a long time (one and one half to four weeks) If the material is contaminated, the addition of 400 mg of a sulfonamide to the medium may give a pure culture of leptospiras (Stavitsky 1945)

To demonstrate the leptospiras by means of test animals young guinea pigs 150 to 200 Gm should be used preferably also young hamsters because these animals are sensitive to leptospiras (*L canicola*) which are only very slightly pathogenic for guinea pigs (Randall 1948)

The inoculation should be made into the peritoneal cavity with 0 5 c c of blood Daily examinations from the third day on may show leptospiras even in those cases in which the strain does not cause the animal to become sick If the animal develops fever the blood is usually positive and pure cultures may be obtained by inoculation of the blood obtained by puncture of the heart, into suitable media Guinea pigs dying of leptospirosis show hemorrhages and mostly a severe jaundice At autopsy the liver and kidneys sometimes contain leptospiras in abundance in other cases very few or none are found The adrenals are always positive

White mice are also used they are susceptible to many strains of leptospiras but one must bear in mind that white mice may also be spontaneously infected as first described by Bessemans and Thiry (1929) and later by Schuffner (not published) Ruys Mankenhof and Wolff (1948) found two colonies of white mice to be heavily infected with *L ballum* which were excreted in very large quantities One must be sure that the colony of mice in use is free from spontaneous infection Bessemans Thiry and Tiellin (1933) demonstrated that some strains of *L icterohaemorrhagiae* kill the mice quickly and that others cause practically no symptoms except a constant urinary excretion of leptospiras virulent for guinea pigs

Leptospiras in Urine

Leptospiras may appear in the urine from the beginning of the second week of the illness on Direct examination in the dark field sometimes shows the leptospiras in great numbers If the urine is acid most of them will be dead and will show the typical rigid appearance Passage through a susceptible animal (guinea pig hamster) is necessary to isolate them from the urine The patient should be given an alkalinizing diet a few days before the specimen is to be collected to prevent the damage of acid urine The simplest way to obtain a positive result is to take the second portion of urine of the day and to inoculate the animals intraperitoneally with one cubic centimeter of the freshly excreted urine at the bedside of the patient Urine sent to the laboratory seldom contains living leptospiras

Leptospiras in the Cerebrospinal Fluid

As early as 1916 Costa and Troisier described a case of Weil s disease in which the principal symptom was meningitis Since that time the involvement of the meninges as a constant and sometimes predominant symptom of leptospiral infection has become well known There is however, no correlation between the seriousness of the clinical symptoms and the pathologic changes or the presence of leptospiras in the spinal fluid

There are a number of other strains which have been more or less exhaustively examined *L bovis*, *L vituloreum*, *L icterohaemoglobinuriae L schüffneri L mukingilwa*, *L andaman* A, the strains H and H C Veldrat Semarang 173 Djasiman and many others Our knowledge of either the serology or the epidemiology of these organisms however, is still too incomplete to include in Table XII

Variability

So far as I know no variation in serologic behavior has ever been observed The old strains from the Amsterdam collection have all remained stable No conclusive animal experiments have ever shown a transition of one type into another The experiments of Uhlenhuth and Zuelzer (1922) and of Baermann and Zuelzer (1923) who considered the various strains to be all variants of one classical species are open to criticism

Van Riel (1946) however basing his conclusions on his experiments in Africa with a number of strains but not with all types now available defends the thesis that intermediate types exist and that there are transitions from one type to another He emphasizes that strains which belong serologically to *L grippotyphosa* in Central Africa cause a disease with frequent jaundice and a high death rate However as long as no exhaustive study of the epidemiology has been made the picture is not complete and conclusions are premature

DEMONSTRATION AND ISOLATION OF LEPTOSPIRAS

In all leptospiral infections the microorganisms circulate in the blood during the first week of the illness After the first ten days positive blood cultures are very rare Bone marrow has been found positive even on the twentieth day (Dreyfus and Montefiore 1939) In the latter phases of the disease the leptospiras may be excreted with the urine Sometimes the spinal fluid contains leptospiras in incipient stages At autopsy both the liver and the kidneys may contain leptospiras

Leptospiras in the Blood

Blood films stained with Giemsa stain very rarely show leptospiras Ordinary dark field examination of blood also rarely gives a positive result and many so called positive findings have been caused by pseudoleptospiras mistaken for actual leptospiras With the centrifugal method however leptospiras may be demonstrated in the blood in some cases during the first days of the illness (Ruys 1933)

For this purpose one part of a 1 per cent sodium oxalate solution in phosphate buffer pH 8 1 is mixed with 9 parts of blood The mixture is then centrifuged for 15 minutes at 1500 r p m The clear plasma is examined under the dark field microscope with low magnification If no leptospiras are found the remainder of the plasma is centrifuged for 20 minutes at 10 000 r p m The sediment may show the leptospiras Blood collected in Liquoid Roche (15 to 20 c c blood in 4 c c of a 1 per cent polyanethol sodium sulfonic acid solution in saline = Liquoid) can be used also for dark field examination after the first centrifugation and sediment can be obtained from the plasma (van Thiel 1948)

It is unfortunate that this rapid method which permits an early diagnosis within half an hour after the sample has been taken is not absolutely reliable In several cases microscopically negative blood specimens yielded positive cultures or animal inoculations On the other hand no other method gives so quick an answer so early in the disease All three methods should be used to

Strong co reactions are however often observed and in these cases absorption tests are indicated (see also Ruys Minkenhof and Wolff 1948) Sera of patients infected with the incomplete biotype of *L icterohaemorrhagiae* may show titers against *L canicola* which are as high as and at certain moments even higher than against the causative strain This nonspecific titer rises more quickly and disappears *sooner than the specific one* so that in convalescence the titer against the causative strain is always the highest Even a rising titer against a certain strain in itself however is no proof that this strain is the etiologic one

The absorption test gives immediate and more reliable information

A titer below 1 1000 may indicate that the causative species was not included in the series of strains used for the tests it may be only a co reaction In convalescence the titer drops but the serum may react positively for years after the illness be it only in low dilutions (1 30 to 1 300)

In Sumatra Wolff (1936) found the reaction negative one year after the disease in most cases Low titers always indicate further careful examination

Patients who have been treated with immune serum at the beginning of the disease form antibodies only very slowly and high titers are not reached at all (Schuffner 1942) The serologic diagnosis can be conclusive only if all sources of error have been considered and excluded

Antibodies in Urine

In addition to the antibodies in the blood the urine also may contain specific agglutinins and lysins (van der Hoeden 1936) Formalinized cultures should be used for nonsterile urines The concentration of antibodies has no relation to the presence of albumin in the urine The titer of the urine is lower than that of the blood In a few cases it was only 1 2 but it may rise to 1 256 Co reactions are much rarer with urine than with sera

Antibodies in Spinal Fluid

In some cases of leptospira infections the spinal fluid contains antibodies but seldom in larger quantities Walch Sorgdrager (1938) found that undiluted spinal fluid was never positive in eleven patients with Weil s disease with and without meningeal symptoms Gsell (1946) however, mentions positive results in low titers from the second week of the illness on especially in cases with serous meningitis The titer varies between 1 2 and 1 100 and sometimes it is even higher than 1 100 A titer of 1 10 is considered proof of the infection

GENERAL REMARKS

The various methods outlined above make an etiologic diagnosis possible either by isolating the causative agent or by serologic examination A refined serologic technic is often required The question has often been raised

In all cases of Weil s disease or canicola fever in Amsterdam Minkenhof could demonstrate a serous meningitis in the second week while in only a few cases was the number of cells high Gsell and Rimpau (1944) stress that in the various leptospiral forms of meningitis during the first days of the illness no inflammatory changes can be observed despite distinct meningeal symp toms They always appear in the second and third weeks however Only rarely can the leptospiras be isolated from the spinal fluid Schuffner and Walch Sorgdrager (1936) found them only in one out of twenty five cases of Weil s disease with meningeal symptoms Cultures and animal inoculations are indicated when it is necessary to examine spinal fluid

Leptospiras in Post Mortem Material

The demonstration of leptospiras at autopsy may be possible by dark field examination of smears from the liver kidneys or adrenals In tissues the silver impregnation by the Levaditi method* will show the leptospiras in these organs Cultures will be possible only immediately after death In all other cases animal passage is necessary In chronic animal carriers (rats dogs mice but not rabbits or man) the process in the kidneys is sharply lo calized to limited parts of the cortical substance leptospiras will be found in layers on the epithelium of the convoluted tubules Several parts must be examined before a diagnosis of leptospiral infection can be excluded (Schuff ner and Kuenen 1923)

Leptospiras in Surface Water

Surface water is often the source of infection with leptospiras (Weil s disease mud fever) but it is very difficult to demonstrate these microor ganisms in the water Microscopically they cannot be distinguished from the nonpathogenic *L biflexa* which is often found in water

The only reliable method to date is that of van Thiel and co workers who bring the warmed water (37° C) into immediate contact with the tissues of susceptible animals either by bathing guinea pigs with an abraded skin in the suspected water or by letting this water flow through the subcutaneous tissue of the animal By this method even very small numbers of pathogenic lepto spiras can be isolated from the water

SEROLOGIC DIAGNOSIS

If no leptospiras have been isolated from the patient the diagnosis can be made serologically in a number of cases The antibodies do not usually appear before the seventh to tenth day of the illness They then increase rapidly and reach the highest titer in the third or fourth week The reliability of this method depends to a great extent however on the number of strains with which the serum is tested

If there are no co reactions and the titer has risen to 1 1000 or more during the course of the illness the probable cause of the disease may be established in this way

*The editor (R. B H. G) prefers the Krajian method as outlined in Chapter 70

As long as the epidemiology of the various types or species has not been sufficiently clarified we think it necessary to keep them separated even though only provisionally for some

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whether it is necessary to go so far in serologic differentiation and whether the diagnosis of a leptospiral disease without further differentiation would not be enough

A typical case of Weil's disease may be recognized as such by its sudden onset high fever, conjunctival injection muscular pains jaundice albuminuria and meningeal symptoms The death rate is high However the mistake of Noguchi's co workers who mistook cases of Weil's disease for yellow fever, is too well known

Since more attention has been paid to the frequent occurrence of less typical cases we know that practically all leptospiral infections produce in principal the same clinical picture

In infections with some strains jaundice is frequent (Weil s disease *L bovis)*, with other ones it is rare *(L canicola, L grippotyphosa)* other groups are intermediate Serous meningitis is a predominant feature in some *(L canicola L pomona)*, in others it is not often described The renal and extra renal disturbances which influence the production and composition of the urine (Klarenbeck and Schuffner 1933) may be severe *(L icterohaemorrhagiae, L bovis L icterohaemoglobinuriae)* or practically absent *(L canicola, L grippotyphosa)* On the whole the differences are in degree never essential The pathogenicity of the various types or species for experimental animals is not the same but this quality is not essential either Thus far the only reason but a very important one why differentiation seems indicated is the difference in epidemiology The serologically different strains often show a quite distinct parasite host relationship and hence a typical epidemiologic behavior (see also Table XII)

L icterohaemorrhagiae lives in the kidneys of the rat *(Rattus norvegicus norvegicus Rattus rattus alexandrinus)* where it may persist for the whole of the lifetime of the animal *L grippotyphosa* is found in the kidneys of the vole but after a longer or shorter period the animal may be free of it (Schuffner and Bohlander 1943) *L canicola* is found only in the dog as a carrier *L pomona* in Switzerland is found in infections of swine (Gsell 1946) *L hebdomadis* is confined to *Microtus montebelloi* in Japan and to dogs in Medan

Sometimes it is difficult to decide whether finding a certain animal as a leptospira carrier is mere chance or whether it means that this is the real animal host and the reservoir which enables the parasite to persist During the last years several diseases have been recognized as leptospiral infections for example swineherd s disease in Switzerland *(L pomona)* jaundice in Palestine *(L bovis)* a part of the cases with serous meningitis *(L canicola, L pomona L sejro L grippotyphosa)*, and many diseases in the Belgian Congo and Australia Several animals have been found to be carriers It will take some time and much work before we know how far minor differences in serology are accompanied by distinct epidemiologic behavior

The complete and incomplete biotypes seem to behave practically alike in all respects and therefore all groups are considered to belong to the same species

CHAPTER 14

WEIL'S DISEASE

ARDZROONY A. PACKCHANIAN

DEFINITION

Weil's disease or leptospirosis is an infectious disease caused by *Leptospira icterohaemorrhagiae* and characterized by sudden onset of fever, headache, nausea, vomiting, muscular pain, jaundice and hemorrhagic tendencies. Weil's disease is not to be confused with catarrhal jaundice or epidemic infectious hepatitis, for which a virus etiology has been suggested.

ETIOLOGY

The causative agent of the disease is a finely coiled spirochete which is now universally known as *Leptospira icterohaemorrhagiae* (Inada et al., 1916). See Chapter 13.

EPIDEMIOLOGY

Leptospirosis is world wide in distribution, occurring usually sporadically, but occasionally in small or larger outbreaks.

Wild rats (*Rattus norvegicus, Rattus rattus alexandrinus* and *R. rattus rattus*) are the chief reservoir hosts of *L. icterohaemorrhagiae*. Once these rats become infected, they serve as carriers of leptospiras throughout their lives, eliminating the microorganisms in the urine. This contaminated urine serves as the principal source of human infection. Dogs and mice (*Mus musculus*) have been found to be infected with typical *L. icterohaemorrhagiae* and may serve as a source of human infection (Packchanian, 1938). The leptospiras gain access to the body through mucous membranes or abrasions of the skin which have come in contact with water or other substances contaminated by the excreta of infected animals. Occupations that place people in environments habituated by rats and that are conducive to skin abrasions are associated with a strikingly higher incidence of Weil's disease. Miners, fish cutters, and employees of breweries, sewage disposal plants, garbage disposal plants, abattoirs and wharves most commonly contract the disease (Packchanian, 1941; Stiles and Sawyer, 1942).

PATHOLOGY

The most striking gross pathologic findings are hemorrhages and jaundice. Large hemorrhages are commonly found in the subcutaneous tissues, the viscera, pleura, or peritoneum, small or focal hemorrhages are found in almost all tissues. The liver and kidneys are generally enlarged to a moderate degree.

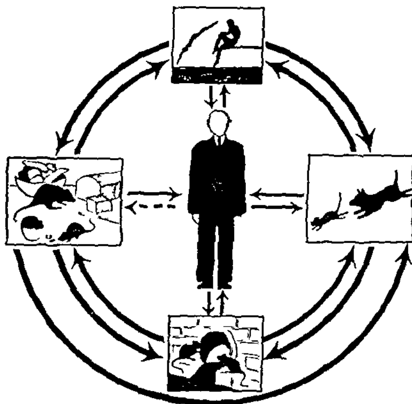
Microscopically, the liver shows changes varying from cloudy swelling to focal necrosis. Minute hemorrhages, disruption of the liver cell cords and

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ment may be revealed by oliguria or anuria and azotemia The more severe cases present a *hepatorenal syndrome* and a typical uremic state may be the final picture in the fatal cases

WEIL'S DISEASE

(ICTEROHAEMORRHAGIC LEPTOSPIROSIS)



the cycle of infection

Fig 110—Cycle of infection in Weil's disease (icterohaemorrhagic leptospirosis)

LABORATORY FINDINGS

In the clinical cases of Weil's disease there is usually a leucocytosis of 10 000 to 20 000 or more with a moderate increase in the polymorphonuclear leucocytes Albuminuria is a rather constant finding and a microscopic *hematuria is frequently noted Nitrogen retention is evidenced by* an increase in the nonprotein nitrogen and blood urea nitrogen The icterus index is elevated at times to about 300 A biphasic van den Bergh reaction is typical but not constant The urine *shows an increased concentration of urobilin* and has been shown to contain bile late in the illness

dilatation of the sinusoids are also commonly seen The kidneys present de generation and necrosis of the epithelial cells of the tubules lymphocytic in filtration and small hemorrhagic foci in the stroma If the necropsy is per formed soon after death before post mortem changes have taken place and tissue sections are made and stained by the silver stain of Levaditi or Warthin * one may find large numbers of leptospiras in the intercellular spaces especially of the kidneys and liver

SIGNS AND SYMPTOMS

After an incubation period of seven to fourteen days the disease is com monly ushered in abruptly with a chill and pyrexia of 102° to 104° F (39° to 40° C) with headache and prostration Nausea and vomiting are fre quently present and general muscular pain is characteristic Petechial hem orrhages are sometimes observed in the skin conjunctivae and oral mucosa

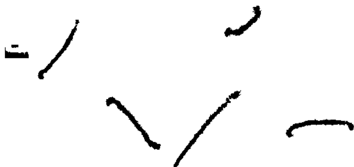


Fig 109 —*Leptospira icterohaemorrhagiae* from a culture Dark field illumination (Approxi mately ×4500)

There may be epistaxis hemoptysis and hematemesis in the more severe cases Conjunctivitis and photophobia are not infrequent findings Hiccup is often a persistent and an annoying symptom Delirium and signs of meningeal ir ritation are sometimes prominent features In most cases jaundice develops on the third to fifth day after the onset The intensity of the icterus and other symptoms varies greatly with the severity of the illness and probably many cases present very little or no jaundice at all In the milder cases the fever terminates soon after the jaundice appears In the more severe cases there may be a period of normal temperature followed by a secondary rise or the temperature may remain elevated for ten to twelve days The liver becomes large and tender the spleen usually is not palpable Renal impair

*The editor (R B H G) prefers the Krajian stain Chapter 70

from catarrhal jaundice and yellow fever was quite difficult, and some incorrect diagnoses have been made. For a summary of the differential diagnosis of these three diseases see Table XIII.

TABLE XIII. DIFFERENTIAL FINDINGS OF YELLOW FEVER, WEIL'S DISEASE AND INFECTIOUS HEPATITIS

	YELLOW FEVER	WEIL'S DISEASE	INFECTIOUS HEPATITIS
Etiology	Virus	Leptospira	Virus
Transmission	Bite of mosquito	Usually through skin abrasion	Contact (droplet and water)
Reservoir host	Man, wild animals	Rats (Rattus)	Man
Geographic distribution	Africa, South America	World wide	World wide
Person [illegible]	[illegible]	[illegible]	[illegible]
Occupa[illegible]	[illegible]	[illegible] sions	[illegible]
Occurrence (Morbidity)	Small or large epidemics	Sporadic	Sporadic and large or small outbreaks
Mortality	Usually high	Probably less than 5%	Probably less than 0.1%
Nature of pain	Severe muscular pain	Generalized muscular pain	Slight epigastric pain
White blood cell count	Decreased	Increased	Not changed
Culture test		+	−
Inoculation of Mus musculus	+	Carrier	
Inoculation of deer mice *(Peromyscus maniculatus gambeli)*	+	++	Not susceptible
Guinea pig	+	+	Not susceptible
Agglutination test with leptospira		+	
Mouse protection test *against yellow fever* virus	+	−	−
Post mortem findings	Hepatic necrosis	Leptospiras in kidneys, liver	Catarrhal inflammation of liver

PROGNOSIS

The mortality rate in Weil's disease is rather low. Although some workers report figures as high as 30 per cent, these statistics are based mostly on hospital admissions, which include only the more severe cases. Considering cases of all degrees of severity, the mortality rate is probably less than 5 per cent. Convalescence is likely to be prolonged.

TREATMENT

Although many drugs (arsenicals, bismuth, antimonials and sulfonamides) and antibiotics (penicillin and streptomycin) have been tried, there is no specific chemotherapy for Weil's disease at the present time. A commercial polyvalent antiserum is available and has been used with some good

DIAGNOSIS

Since there are other clinical entities which may give a similar clinic[al] picture, the absolute diagnosis of Weil's disease can be established only b[y] specific laboratory methods These consist of (1) direct microscopic dem[onstration] of *L icterohaemorrhagiae* in the blood or urine, (2) guinea pig o[r]

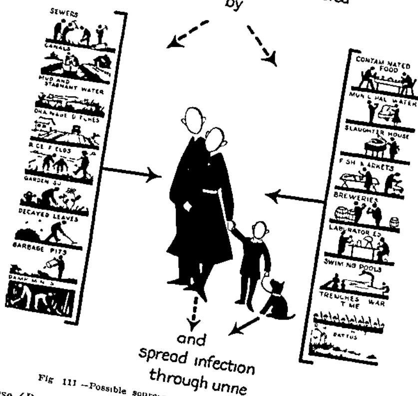


Fig 111 —Possible sources of infection in Weil's disease

[dee]r mouse (*Peromyscus maniculatus gambeli*) inoculation with blood or urine [of b]oth (3) culture of the microorganism from the blood or urine specimens [of t]he patient, (4) serologic reactions, (5) demonstration of the organism [micr]oscopically in stained sections of the viscera of cases terminating fatally [(C]hapter 13

[I]n the past when the laboratory methods for diagnosis of Weil's disease [were] not fully developed, the differentiation of Weil's disease particularly

CHAPTER 15

FEVERS DUE TO RATBITE (INCLUDING SODOKU)

ARTURO CURBELO HERNANDEZ

In addition to the trauma caused by the common or laboratory rat, there often follows infection with specific bacteria introduced through the bite Two of these have been described *sodoku disease and Haverhill fever* These two forms are clinically similar, although the causative agents described in each are entirely different Sodoku and ratbite disease were formerly considered synonymous, but later studies and improved technical bacteriologic methods have changed the older concept by *defining Haverhill fever as a separate entity*

Sodoku is caused by a spirillum *(Spirillum minus)*, while Haverhill fever is due to a pleomorphic bacillus *(Streptobacillus moniliformis)*

HISTORY

That disease may follow a ratbite has probably been known since ancient times (Francis 1932a), although references to it are from a relatively recent period The first clinical work is that of Ives in 1831 and of Wilcox in 1839 It was not until about 1900 that Miyake (1900) gave a reliable description of ratbite fever as a clinical entity Later, Ogata (1908) referred to this same entity but introduced into the nomenclature the word "sodoku," the Japanese name for the disease Then descriptions and references by other authors appeared (von Ofenheim, *1909, Shikami, Horder, Middleton, 1910, Proescher and* Hata, 1912), outlining the clinical features of the disease, now differentiated with relative ease from other entities and undoubtedly due to a true bacterial infection Hata (1912) recommended treatment with arsenicals because of its resemblance to syphilis Today this treatment is used for the spirillary form, sodoku

Recently, numerous investigations have been carried out by different authors to demonstrate the cause of the disease, in this way numerous microorganisms have been isolated from the few cases studied *Staphylococcus aureus* (Miyake), *Neosporidium, Sporozoa muris* (Ogata), the *Micrococcus tetragena* (van Ofenheim), a *Telosporidium* (Shikami), and *Bacillus septicomuris* (Proescher) Some of these authors successfully inoculated laboratory animals, especially guinea pigs, but in general the investigations were not sufficiently conclusive nor was *the identity of the causative agent proved*

Bacteriologic investigations began to bear fruit with the classical report of Schottmuller (1914), who isolated a Streptothrix He called this *Streptothrix muris ratti* This investigator also reported a similar organism *(Streptothrix teraxerus cepapi)* from a second case, in a patient bitten by an African squirrel *(Teraxerus cepapi)* This investigation marks the beginning of bacteriologic progress in the study of ratbite fever

In 1916 a curious event occurred, in two consecutive numbers of the same medical journal two studies appeared on the etiologic factor of the disease One of these, by Blake (1916), appearing in the January issue, established the relationship of *S muris ratti* previously described by Schottmuller, to the disease, the other study by Futaki, Takaki, Taniguchi, and Osumi (1916), in the February issue, reported a new spirillary organism later called *Spirochaeta morsus muris*

The author wishes to express his gratitude to Dr A Anido Dr A Hernández Dr F Rio Leon and Dr D Velasco *of Santa Clara Cuba for* data included in this chapter

results, however, an insufficient number of human cases have been so treated for a correct evaluation of the serum Convalescent serum if obtainable, is probably of some value

The symptomatic treatment is the primary concern Maintenance of the fluid electrolyte balance is of utmost importance When the patient is able to retain food a high protein high carbohydrate diet with vitamin supplements is recommended Recently methionine has been used in cases of Weil's disease on the assumption that this compound protects the liver from damage

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blood and are demonstrable in all cases if a diligent search is made As the process advances, other symptoms are found which are characteristic of this infection, such as falling out of hair in the ocular region associated with intense keratoconjunctivitis. Ulceration of the skin may also occur At the end of the fifth week the animal dies, spirilla are demonstrable in the blood in the lymph glands, spleen, kidneys, adrenals, and even in subcutaneous tissue

Intraperitoneal inoculation in the mouse does not produce the same picture as in the guinea pig Practically no clinical manifestations are produced, even after one or two weeks, the period of incubation in the guinea pig *Spirilla* appear in the blood, at first scanty, then in greater numbers The presence of organisms in the circulation of the mouse is maintained for a long time, but the animal does not succumb to infection The rat reacts in the same way as the mouse, although the mouse is preferred for demonstration of the microorganisms in the blood

Other rodents are also susceptible For practical purposes the guinea pig is the animal of choice Monkeys and rabbits also may be used



Fig 112 —*Spirillum minus* *A* to *F*, from lymphatic gland of human patient. Flagella can be easily seen *G* to *I* from blood of a guinea pig *A* to *F*, Giemsa stain, *G* to *I*, Fontana stain

Transmission.—The permanent reservoir of the organism is the rat and perhaps other Muridae which infect each other probably by bite or by ingestion of cadavers of those of the colony that have died and have been devoured by the others Conjunctival fluid may act as a transmitting medium as well as the ectoparasites so common in these animals

The bite of other animals (dog, cat, hutia, etc) may be infectious if the animal has been bitten by a rat, but these other animals may serve as occasional reservoirs of the disease Transmission by this means is exceptional

Transmission may occur by mouth, although this is rare This type of transmission was demonstrated (Laroderie) in a case of a soldier in World War I, in 1914, who ate a rat on a bet (Nevot, 1935)

Thus we have seen that transmission of sodoku may occur by animal inoculation and in various other ways, but these are exceptional in comparison with the natural manner, which is through ratbite

This spiral shaped organism which was described by the Japanese investigators became known more generally as *Spirillum minus*, according to Robertson (1924), who identified it as the species described by Carter in 1887 as the first spirochete isolated from rodents. Its taxonomic position has not been determined as yet, due to difficulties in the cultivation of this organism (Bergey, Breed, Murray, and Parker Hitchens, 1939)

Concerning the bacillary agent the facts are more definite. The *S muris ratti* of Schottmuller, confirmed by Blake also in a case of ratbite fever, has been observed by other investigators under different conditions. Tunnicliff isolated this microorganism from the lungs of rats with bronchopneumonia (1916a). Litterer (1917) used the term "Streptobacillus" for the first time in cases of ratbite fever in human beings. Dick and Tunnicliff (1918) found it in a case of weasel bite, Jones (1922) from the lungs of rats with pneumonia. Levaditi, Nicolaou, and Poincloux (1925) isolated *Streptobacillus moniliformis* from a clinical case not due to ratbite (erythema multiforme), without associating it with the Streptothrix of Schottmuller. This was undoubtedly the same organism. It was also isolated by Lemierre et al (1937) and others from the blood in a typical case of ratbite fever, thus reaffirming the fact that *S moniliformis* is a causative factor for the disease.

In 1926, Place, Sutton, and Willmer reported an epidemic in Haverhill, Mass. They isolated from the patients' blood and joints a microorganism for which they created a new genus which they called *Haverhillia multiformis*. The epidemic resulted from the use of unpasteurized milk. Later, this organism and this disease were apparently associated with ratbite (Dodd, 1926, Hazard and Goodkin, 1932, Scharles and Seastone, 1934). This led to the conclusion that the three microorganisms described under different circumstances in different countries and in different languages were identical (Brown and Nunemaker, 1942)

The suggestion made by Brown and Nunemaker to keep the name *Streptobacillus moniliformis* appears to be most pertinent, and the greater part of the most recent investigations have utilized this designation.

INFECTION BY SPIRILLUM MINUS (SODOKU)

Spirillum Minus Carter

Synonyms.—The bacterium has been described as *Spirochaeta morsus muris*, *Spirillum minus*, *Spirochaeta muris*, *Spirochaeta laverani*, and *Spirochaeta petit*. The first two terms are frequently found in the literature, the majority of authors preferring the term *Spirillum minus* Carter.

Morphology.—The organism is a short thick spirillum, measuring from 2 to 5 microns in length. It has pointed extremities, with one or more frequent and readily demonstrable flagella. The spirals are short and clearly visible in well made preparations. They are 1 micron in length and are rigid and regular. They are very motile, in this respect resembling vibrios.

Staining Characteristics.—The microorganism stains well with aniline dyes, and also with the usual blood stains. This facilitates their study in the blood, lymph, etc.*

Culture.—*S minus* has not been successfully cultivated in ordinary media. Observations must be made of the tissues of infected human subjects or inoculated animals.

Experimental Pathogenic Action.—It is very difficult to demonstrate this organism in man. Use of animal inoculation is preferable for diagnostic purposes.

From the experimental point of view, the guinea pig is the animal of choice in the study of sodoku disease, and the preferred routes of inoculation are cutaneous (scrotal), subcutaneous, and intraperitoneal. When inoculated with material from the patient (blood or lymph from a lesion or regional gland fluid), after an incubation period of one to two weeks, the guinea pig develops fever accompanied by glandular enlargement and marked reaction of the subcutaneous tissue of the anogenital region, especially apparent in the scrotum and prepuce of the male and the labia of the female. Spirilla appear in the

*The Krajian stain is recommended by the editor (R B H G)

CLINICAL PICTURE

There is rapid healing of the wound unless secondary infection interrupts the process This rarely occurs since physicians as a rule treat the wound locally *with antiseptics or antibiotics* Such local treatment however is useless in spirillary infections because these infections are too deep seated for the antibiotics to reach them If prophylactic treatment is desired at this point it is necessary to cauterize as deeply as the limits of the toothmarks of the animal In this way the development of sodoku may be prevented

The period of *incubation from the time the bite is inflicted until the* appearance of the first symptoms is variable averaging fourteen to fifteen days Periods as short as forty eight to seventy two hours have been cited and also long periods of about thirty days In one case the development of the local lesion from the time of the bite to the appearance of the first symptoms was just twenty four hours (Anido Hernandez Rio Leon and Velasco)

SYMPTOMATOLOGY

The disease begins suddenly History of a bite should immediately suggest the possibility of this disease At times the prodromal symptoms occur at the site of the bite mild edema reddening infiltration paresthesia the last however is not constant The symptoms may be divided into the fundamental groups (1) local symptoms and (2) general symptoms

Local Symptoms

Local symptoms are divided into two groups those which occur precisely at the site of the bite and those which affect the tissue next to the bite

Soon after the bite pain begins at the site of the bite followed by swelling and reddening with the formation of an *inflammatory nodule* *Edema develops* around the lesion which extends to neighboring tissue According to the intensity of this edematous infiltration the nodule takes on various colors terminating in ulceration due to focal necrosis A zone of lymphangitis is produced around the lesion

From this point spread more or less nodulated strands of lymphangitis which extend throughout the tissues of the region The regional glands are infiltrated and very painful and are accompanied by an inflammatory periadenitis Suppuration rarely occurs *Adenitis* is *sometimes so discrete* that it is very difficult to find it

General Symptoms

General symptoms may be considered as of five groups (1) fever (2) *exanthem* (3) nervous manifestations (4) pain (5) symptoms in other organs

Fever—Fever begins suddenly, as high as 40° C or more although in some cases it may be moderate with slow elevation Frequent chills occur with each thermic elevation This *febrile period averages three* to four days in duration followed by a second apyretic phase which may last about five days

PATHOLOGY

At the site of the bite, there occurs an area of intense cellular infiltration edema and marked degeneration leading to necrosis Fibrous production involves the different structures and connective tissue leading to sclerosis

Kaneko and Okuda (1917) described the following lesions renal congestion and epithelial degeneration of the tubules fatty degeneration of the liver



Fig 113 —Sodoku Chancre of inoculation Necrosis can be seen



Fig 114 —Sodoku Chancre of inoculation Heavy infiltration of tissue around the site of the bite

with central lobular necrosis with hyperemia and isolated hemorrhages congestion of lymphatic glands with interstitial hemorrhage diffuse pulmonary congestion intense medullary hyperplastic reaction hyperemia meningeal edema and desquamation of the bladder epithelia Spirilla can be observed in the lesions principally in the adrenals and in the liver

Lesions found in guinea pigs which have died of sodoku are on the whole, similar to those described in man without the special characteristics which may prove of some value in diagnosis

As to the cardiovascular apparatus aside from the tachycardia which accompanies the fever the majority of the patients show a marked lowering *of blood pressure*

There are definite blood changes There is almost constantly a certain degree of anemia this may be marked with a decrease in the hemoglobin The red count also decreases Rarely is there an increase in the number of red cells

Leucocytosis occurs although not high fluctuating usually between 10 000 and 20 000 although in some cases it may be as high as 40 000 This occurs in the febrile periods In afebrile periods the leucocyte count drops markedly sometimes as low as 4 000 In these cases with the return of the febrile period the leucocyte count rises again This is a fairly regular observation

The differential count shows changes that are especially noteworthy first there is an increase of neutrophilic leucocytes with a normal number of mononuclears An outstanding observation is the eosinophilia which may be *rather high Variations of these counts may be due to other conditions which* may be present in some cases

As to serologic reactions currently used in the diagnosis of syphilis (Wassermann Kahn Meinicke) the authors disagree However a positive reaction in the absence of syphilis may aid the diagnosis since it is possible to accept the theory of certain antigenic affinities among spirillary micro organisms

In the serum of these patients there may appear spirochetolytic sub*stances demonstrable by the Pfeiffer phenomenon*

COURSE

The disease shows various phases of activity each one progressively less intense It may last for weeks or months exceptionally even longer

In general the disease except in particularly serious cases tends toward recovery However this development may be hastened by adequate treatment as soon as diagnosis has been established When diagnosis is in doubt the disease may run its *full course a rare occurrence at the present time*

LABORATORY DIAGNOSIS

Laboratory investigations consist of the following

(1) Test for Presence of the Spirillum in the Patient

(a) In the blood principally during the febrile periods although this is difficult

(b) At the site of the bite either by obtaining lymph or by section of the inflamed tissue

(c) In the lymph at the site of the exanthem

(d) In the lymph glands in the lymph as well as in sections of tissue

This gives the characteristic recurrent aspect to the fever curve Numerous variations can be produced however in the different paroxysms varying in different cases At times the period of recrudescence is often marked by a subfebrile state at times by a continuous fever

Exanthem—Exanthem is an almost constant finding in the development of the disease In some cases it is located so close to the site of the bite that it may almost be missed The tendency is toward generalization but it may be localized in certain regions without special or marked predilection for any one area

The type of lesion is rather variable It may be a simple macular lesion or maculopapular or papular or even nodular The general appearance resembles the cutaneous lesions of syphilis or rubeola

The color of the lesion may vary from pale pink to violet red and may even appear ecchymotic

The size of the lesion varies sometimes it is as much as an inch or more *in diameter There is no particular tendency to confluence* but *occasionally* this may occur in large patches with irregular borders

These exanthematous lesions show a very definite characteristic—they are painful with or without pressure Sometimes the pain may appear before the lesion is visible The lesions are not pruriginous

Spirilla may be found in lymph obtained from these lesions

The exanthem is marked in the febrile period and diminishes in intensity to the point of disappearance in the intermediate intervals As the disease progresses the exanthem becomes progressively lighter in intensity

Nervous Manifestations—Nervous manifestations sometimes characterize a clinical type of the disease when they are very marked The prognosis may be guided by the severity of the symptoms These may range from the mild disease to the most serious type There may be stupor exhaustion prostration and coma (in fatal cases) Such disturbances as paresthesias as well as motor disturbances characterized by dystonia may be present These disturbances may be exaggerated diminished or totally absent

Pain—Pain is always associated with location in the different muscle groups of the limbs abdomen and thorax also bones and joints may be affected

Symptoms in Other Organs—Certain organs are not affected by the disease among these are the heart spleen liver and lungs In general the disease does not follow typical or regular localizations

Some authors have reported the presence of spirilla in the urine suggesting localization of the disease in the kidney Although albuminuria is constant it is slight no other abnormal constituents appear in the urine

In some cases diffuse bronchitis may be present accompanying febrile paroxysms of the disease

As for involvement of the digestive apparatus symptoms include buccopharyngeal exanthem dysphagia anorexia nausea constipation etc Of these only the exanthem and dysphagia are of sufficient constancy to be clinically significant

and Parker Hitchens, 1939), *Actinomyces muris Topley and Wilson* (Wilson and Miles, 1946), and others Utilization of only one name for the infections caused by this organism will be of advantage in future investigation

Origin.—To date, *S moniliformis* has been isolated from different parts of the body such as the *blood and other secretions* and tissues in cases of bite by rats and other rodents the lungs of rats and other sick animals, the nasopharynx of laboratory mice, and *in cases in which* the infection has occurred through other means such as in Haverhill fever

Morphology—Morphology of this microorganism has been well described by various investigators (Levaditi, Litterer, Parker and Hudson, *etc*) *It is necessary to recognize* the fact that but few bacteria show such a high degree of pleomorphism

On *Loeffler's blood serum* fine branched filaments may be observed, about 0 5 micron in width, tending to intertwine, later, fragmentation of the filaments occurs, chains of *bacilli and coccoid forms* now appearing The term "moniliform" is adequate, since these filaments sometimes show a fusiform, oval, or spherical thickening, somewhat resembling Monilia These thickenings may have a diameter several times larger than the width of the filament and may project toward one side only The possibility of variation or association with a coccobacillus (organism L) described by Klieneberger (1935) is due to these phenomena



Fig 115 —*Streptobacillus moniliformis* from a 48 hour culture on Loeffler's blood serum medium First Cuban case (Courtesy A J Aballi and J A Martinez Cruz.)

Staining is irregular, it has been described as gram negative and again as gram positive, the latter mostly in young cultures

It is not motile and does not have acid or alcohol resistant forms

Cultural Characteristics—Addition of blood or serum is indispensable for cultivation *of the organism* *On Loeffler's medium* the colonies are light yellow, 0 5 to 0 7 mm in diameter They show a central somewhat elevated zone with a flattened periphery and irregular edges *There is no hemolysis* *They grow better* under anaerobic conditions and in a 10 per cent carbon dioxide atmosphere

Recent studies show that they produce acid slowly in glucose and *salicin* and sometimes also in maltose and lactose They do not form indole and do not change litmus milk, do not produce hydrogen sulfide, and do not reduce nitrates *They give negative results* with the methyl red and Voges Proskauer tests The catalase test is negative

Pathogenic Characteristics—Inoculation of laboratory animals, which is of *great diagnostic value, is effective* in mice which are very susceptible to this bacterium Rats, guinea pigs and rabbits are resistant The rabbit, however at times shows a few inflammatory *lesions, particularly* arthritis

(2) Inoculation of Susceptible Animals

In this case the guinea pig is preferred since it develops a rather typical experimental picture in which spirilla can be demonstrated (See above)

Inoculation of mice does not produce any pathologic picture but spirilla can be demonstrated in the blood and peritoneal fluid

One must keep in mind that spirilla are sometimes found in these laboratory animals

(3) Demonstration of Specific Antibodies in the Serum

Serum of patients or serum from convalescents can be tested for spirochetolytic and spirocheticidal substances This may be carried out long after the infection has passed and may serve in retrospect rather than for study of cases on hand The serum of the patient or a convalescent or a cured subject is used using as controls mice with spirilla in which dissolution and disappearance of the microorganisms have been observed

PROGNOSIS

Prognosis is generally favorable once the diagnosis has been established and adequate treatment applied Mortality is in the neighborhood of 10 per cent

TREATMENT

In 1912 Hata assuming the origin of the disease to be spirochetal recommended the use of arsenicals in treatment Some cases respond to this treatment with marked rapidity while others respond more slowly so that at times it is necessary to repeat a series before complete cure is obtained

A curious observation made by Cuban investigators (Anido Hernandez Rio Leon and Velasco) is that treatment is somewhat more effective when the disease is allowed to develop rather than when begun immediately upon diagnosis This observation is contrary to most experiences with most infectious diseases

Known antisyphilitic mercury and bismuth derivatives have been recommended and used by various authors although in general it is recognized that their action is not as effective as trivalent arsenicals

PROPHYLAXIS

Prophylaxis should be directed to the destruction of the reservoir of the disease that is against the rat This places the problem within the general scope of community sanitation and prophylaxis

INFECTION BY STREPTOBACILLUS MONILIFORMIS (HAVERHILL FEVER)

Streptobacillus Moniliformis (Levaditi)

Synonyms—The bacterium has been described under many different names among which the more important are *Streptothrix muris ratti* Schottmuller (1914) *Haverhillia multiformis* Parker and Hudson (19 6) *Act omyces act no des* Bergey (Bergey Breed, Murray,

Arthritis is as frequent a lesion and symptom as is the exanthem It appears soon after the beginning and is *generally associated with* pain generalized in the limbs especially in children The period of duration of the disease is variable in children it is more transient than in adults in whom it persists much longer sometimes for many years

Other manifestations may be present such as bronchitis cough and dysphagia

The course of the disease has the general character of the infection produced by the bite and occurs in outbreaks which generally recede only to return anew In almost every case the first period lasts from three to five days the patient returning spontaneously to a normal state It is precisely at the moment of the first remission that the exanthem appears After a lapse of two or three days a recrudescence takes place in which the exanthem is more pronounced and there are generalized symptoms of arthritis The process may show an intense or an attenuated development according to the *intensity of this latter manifestation* It may last for several days or weeks Later recurrence of symptoms is variable and is influenced by different forms of treatment

Streptobacillary Infection Due to Ratbite

The *site of the bite* so far as incidence of the infection is concerned does not make any difference in the processes

As to the *period of incubation* at first it was thought that the period was much shorter in the bacillary infection than in the spirillary type but an analysis of the literature shows that there is no essential difference since some cases of bacillary infection may appear quickly (in two or three days after the bite) whereas in others there has been a delay of as long as nine days and in some cases as long as fourteen days and even longer One observation reports a lapse of several months between the time of the bite and the onset of symptoms

The *onset of the disease* is sudden *with fever chills headache and vomiting* In this respect there is no essential difference in the two diseases

As to *local symptoms* the differences are of slight diagnostic importance Similar variations appear in both types Lymphangitis and adenitis may develop as in spirillary infection *though in the latter healing of the wound* between the time of the bite and the beginning of the disease may frequently be observed

Regarding *general symptoms* there is the fever which in a major part of the cases is not very high The fever is of markedly recurrent character although there are some cases in which this is not true In respect to this recurrent character of the fever there is no difference between the two forms of the disease

Exanthem is a symptom which is never absent and as in sodoku has been described by numerous authors It may have characteristics that are quite variable in the different cases The same is true of the spirillary form of the disease

Nervous manifestations show no marked difference in the two forms

Subcutaneous or intraperitoneal inoculation of the mouse is generally fatal within a period of seventy two hours without the production of any characteristic or special lesions The microorganisms are easily recovered by culture from the blood

Variants—There have been isolated from cultures of *S moniliformis* pure forms of an organism similar in appearance to those of the pleuropneumonic group Klieneberger (1935) considers these as symbiotic elements Other investigators (Dienes 1939, Smith 1918 and Brown and Nunemaker, 1942) consider it a variety of the same Streptobacillus

Transmission.—*S moniliformis* can be transmitted either directly by ratbite or indirectly, by means of contaminated food

In the first case the mechanism of the infection is analogous to that of sodoku disease in the second elimination of Streptobacillus in the secretions and excretions of Muridae may explain the mechanism

LABORATORY DIAGNOSIS

Diagnosis of infection due to *S moniliformis* cannot be considered a routine procedure It is based upon demonstration of the organism by culture methods or by inoculation of the mouse a highly susceptible animal and therefore the animal of choice

The Streptobacillus can be demonstrated in the blood of the patient Other body fluids from the patient depending upon the kind of lesion he presents (arthritis abscesses etc) may be used in cultures and inoculations to demonstrate the organism

When the growth in the cultures is sufficient some authors recommend agglutination tests using the serum of the patient from whom the bacillus was isolated Agglutinins when adequate antigen is used do not reach a high concentration but persist for a sufficiently long period of time in the individual

CLINICAL PICTURE

Haverhill Fever Not Caused by Ratbite

The period of incubation in the cases studied was short between one and three days This period is shorter than when infection occurs through a bite

The disease begins suddenly with chills vomiting headache and fever The last symptom is never absent the temperature rises to around 40° C in some cases

One to eight days later an exanthem appears this is one of the most constant symptoms of the disease and persists for a variable period This exanthem is seen principally in the anterior and lateral parts of the extremities One characteristic of this manifestation is that it is found especially around the joints The lesion although not in all cases may also appear in the face and the thorax The eruption resembles rubeola though at times it may be morbilliform Frequently the lesion is of maculopapular aspect dark red in color rounded outline at times with irregular margins varying greatly in form and size (between 1 and 4 mm in diameter), sometimes somewhat larger Petechial hemorrhages may appear in severe cases particularly on the extremities Desquamation is observed in some cases

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Fever Caused by Streptobacillus Monili

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Changes in the blood are practically the same anemia moderate leucocytosis which may be elevated in some cases with increase in neutrophiles, and eosinophilia This last sign is very marked in sodoku

The most marked difference refers to arthritis however this manifestation together with osseous pains has been observed in experimentally inoculated sodoku (Solomon Berk Theiler and Clay 1926 Bayne-Jones 1927, Herschfeld Kibler Colby Koening Schmid and Saunders 1929)

Some authors have tried to establish differences which may be observed clinically between the two entities It is possible that in some aspects a great deal of observation and accumulation of data may do this but in our present state of knowledge we can see how the major part of the symptoms are superimposed and how some cases present variations which are the same in both processes For the moment it is best not to depend upon these data for classification and diagnosis without waiting for results of the bacteriologic investigation

PROGNOSIS

In general the prognosis is good Mortality observed in twelve cases in the United States of America has been 10 per cent

TREATMENT

Neither type responds to specific therapy Conclusions concerning the efficacy of the medicaments which have been used are difficult Autogenous vaccines and the sulfonamides have no action and information concerning these varies Salicylates iodine and quinine have been used with mediocre and equally irregular effect Arsenicals which have a marked action in sodoku show none here although they have not been tried sufficiently to warrant more certain conclusions

The impression gathered from the study of existing bibliography is that treatment is one of the points of difference in the two processes

PROPHYLAXIS

In cases of infection by *S moniliformis* due to ratbite prophylactic measures with slight variations will be the same as those considered in sodoku disease

In Haverhill fever or those cases of infection induced by mouth prophylactic measures should be in the direction of obtaining bacteriologic purity of foods principally milk and milk products The use of pasteurized milk is highly recommended

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Trauma plays an important role in the transmission of framboesia. It *seems likely that the organisms must come in contact with an abrasion* in the skin in order to *initiate successful infection.* It is questionable whether or not they can penetrate the intact skin. *Many patients are able to give a definite history of some previous injury*, others are not. It is generally accepted that the location of the primary lesion is also the site of infection. Primary lesions occur most frequently on those regions of the body exposed and likely to be traumatized, namely the feet and legs. *The ankles (malleoli) and lower* third of the legs are the commonest sites of primary lesions. It is these parts of the body which are most frequently bruised, scratched or cut on persons walking among shrubs and grasses without shoes, stockings or trousers. The drying of mud on the feet and ankles and its subsequent removal is another probable source of abrasions. Crowded, unhygienic living conditions foster the spread of infection in family groups so that frequently all of the children and sometimes the adults in a family develop lesions.

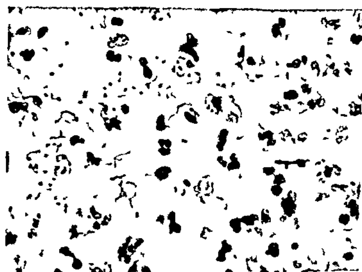


Fig. 116.—*Treponema pertenue* in the epidermis (X970.)

Persons of all ages are susceptible to infection with *T. pertenue*. However in most parts of the world yaws occurs most commonly in children.

The explanation for the higher incidence in children than in adults appears to be mainly in the development of immunity by the latter as the result of previous infection. Contributing factors may be that adults and older children are generally better clad and that adults do not come in direct contact with one another to the same extent as children. Considerable epidemiologic and experimental evidence, *both animal and human, supports* the general belief that among inhabitants of areas where the disease is endemic one attack confers protection against a second. Immunity develops slowly and progressively over a period of years but ... to persist for many years even in the absence of manifest lesions of ... m ch

CHAPTER 16

FRAMBOESIA (YAWS)

ALBERT JOHN SHELDON

Synonyms.—Yaws (English) and pian (French, Spanish, and Italian). Colloquial names: "buba" or "boubas" (Brazil and the Dominican Republic), "cuchipe" (Ecuador), "coko" or "coco" (Fiji Islands), "tonga" (New Caledonia), "puru" or "purru" (Malaya), "lupani" or "tono" (Samoa), "parangki" or "parangi" (Ceylon), "patek" (Java), "momba" (Angola), and "dube" (West Coast of Africa).

CAUSAL AGENT

Treponema Pertenue (Castellani 1905)

The organisms measure 12 to 20 microns in length and have 8 to 20 small, broad turns in the spiral. They are morphologically indistinguishable from *T. pallidum*, the etiologic agent of syphilis. Motility is accomplished by translation in the direction of the long axis, a rotary movement of the spirals, giving the impression of a corkscrew turning on its own axis, and a waving or twisting movement from side to side. The organisms are readily killed by drying and cannot withstand exposure to air and light more than twenty-four hours in a moist medium. Cultivation is difficult, if not impossible.

The spirochetes are present in large numbers in primary and secondary lesions and have been demonstrated in lymph glands, spleen, and bone marrow. They have not been found in the blood stream, but Castellani (1907) successfully infected apes by injecting blood from framboesia patients. Further evidence of their presence in the blood stream is the dissemination of the secondary lesions over the entire body. Organisms have never been demonstrated in deep organs other than those mentioned above, nor in the nodular, ulcerative, scaling, or gummatous lesions of the tertiary stage of the disease. Monkeys and rabbits, as well as apes, can be experimentally infected with framboesia. Hamsters are also susceptible.

T. pertenue organisms are readily transmitted from infected persons to others by direct contact, resulting in a high degree of communicability. Indirect contact with contaminated clothing, bedding, sleeping mats, utensils, furniture, soil, etc., is probably a less important means of spreading disease because of the marked fragility of the organisms. Kumm (1935) showed that mechanical transmission by the minute "gnat" fly, *Hippelates papillipes*, is possible within seven hours after feeding on open framboesia lesions by regurgitation of ingested material containing spirochetes. Venereal transmission does occur but is only incidental. Moss and Bigelow (1922) stated that primary lesions appeared on the genitals in only 1 per cent of 969 cases in the Dominican Republic. In Jamaica, Chambers (1938) reported that less than 3 per cent of 580 primary lesions were located on the genitals, mostly in children under 7 years of age. Autoinfection may occur during the early course of the disease. Lesions frequently spread locally and to opposing contiguous surfaces, particularly around the mouth, anus, and vagina. It is generally believed that congenital infection does not occur. However, Hunt and Johnson (1923) found cases of interstitial keratitis among framboesia patients in Samoa where syphilis does not exist among the natives.

Haitians and Jamaicans and sporadically among Dominicans In 1944, 14,834 cases were reported to the health authorities, and 7,891 were reported through July, 1945

Ecuador—Villagómez (1932) reported that half of the 30,000 inhabitants of the Province of Esmeraldas were infected with framboesia Seventy two cases were reported to the health authorities during the period January August, 1945

Guatemala—Bolaños and Selva (1934) reported having observed three cases of framboesia in Chocolá in 1931 Later many more cases were found in Madre Mia (near Chocolá) in San Pedro Jocopilas, Santo Tomás, La Unión, and Samayac, all neighboring municipalities

Haiti—McKinley (1935) stated that 100,000 cases of framboesia had been reported, the majority from rural districts During 1943, 48,759 cases were reported to the health authorities, 32,195 were reported in 1944, and 11,679 were reported during the period January July, 1945 Duvalier (1945) reported that 97,291 patients attended one rural clinic in Haiti from March, 1943, to March, 1944

Jamaica—Saunders et al (1936) found that framboesia was present in large numbers of persons in St Thomas, Portland, St Mary, St Catherine, Clarendon, St. Elizabeth, and St. James Turner and Saunders (1935) recorded an incidence of 58 per cent in the Bath area and 47 per cent in the Seaforth area.

Nicaragua—Lacayo (1935) reported four cases in Managua

Panama—Brosius (1930) stated that framboesia is uncommon in Almirante where he treated only 12 cases in the previous five years and 4 cases in 1930 Wilson (1934a) reported 424 cases in the province of Darien Later the same year (1934b) he noted an average incidence of 16 4 per cent among five villages near the confluence of the Chagres and Gatuncillo Rivers, about 50 kilometers from the capital city Seven hundred sixty four cases were reported to the health authorities in 1944, and 84 during January June, 1945

Puerto Rico—Gotay, Costa, Mandry, and Payne (1935) found 94 cases among 1,091 inhabitants of a rural section

Venezuela—Cases have been reported from the States of Miranda, Aragua, Guárico, Carabobo, Cojedes, Yaracuy, Portuguesa, Zulia, Trujillo, Mérida, Táchira, Anzoátegui, Sucre, Nueva Esparta, and Bolivar Vegas, Lovera, Itriago, and Medina (1943) reported 24 5 per cent of 236,793 persons infected in Carabobo In 1944, 2 124 cases were reported to the health authorities, and 828 were reported during the period January April, 1945

There is a high incidence of framboesia in equatorial *Africa*, particularly in Liberia, the Gold Coast, Nigeria, French Equatorial Africa, the Belgian Congo, and Angola on the west coast, and in Kenya, Tanganyika, Zanzibar, and Mozambique on the east coast It is common on the Comoro Islands and Madagascar The incidence is fairly high in the Anglo Egyptian Sudan, Uganda, Rhodesia, and Nyasaland There is a low incidence in Algeria, Tripoli (Libya), Egypt, and Kimberley (South Africa)

In *Asia* the incidence of framboesia is high in Assam (India), Burma, Thailand or Siam, French Indo China, Malaya, the Netherlands Indies, and the Philippine Islands It is rare in Bengal and Travancore (India) and is said to be disappearing from Ceylon The incidence in southern China is very low

Framboesia is common in *northern Australia* and on a number of the *Pacific Islands*, namely, Samoa, New Hebrides, New Caledonia, Fiji, Gilbert, Ellice, Caroline, Marianas, and others

PATHOLOGY

Framboesia is characterized by a variety of lesions, some of which tend to occur in a certain sequence Chambers (1938) suggested the following arrangement of the lesions

A Primary stage
  1 Single skin granuloma ("maman pian," "madre buba," or "mother yaw")
  2 Single skin macule or macular patch ("yaws spot")

les ons p rs st for many months after the on et of tl e d sea e and some are subject to suc ces ve crops of les ons o er a per o l of years Wh le the n ajor ty of tl e latter are probably relap e it s po s ble that some may be due to re nfect on Interrupt on of the normal course of the d sea e by treatment seems to retard the development of im mun ty and perhaps shortens the t me before tl e appearance of tert ary les on if any are go ng to develop

In most parts of the orld framl oes a s confined cl efly to Negroes Ho ever Stannus (1935) stated that the Polynes an Melanes an yello v sk nned races Ind an and European ra es a e equally su cept ble to infect on Araujo (19 8) reported that among 30 000 cases in Braz l 15 ° per cent occurred in Negroe 56 ° per cent n me tizos 10 ° per cent in Ind ans and 18 4 per cent in h tes In Cuba Pardo Ca telló (1939) foun l the h te race to be in fected as often as the Negro—°°7 and ° 4 case re pect ely A few ca es have been re ported among h tes n the Un ted States following res dence n or v s ts to trop cal areas where framboes a s en lem Lofgren (1944) reporte l nfe t on n a wh te sa lor ho had con tracted tl e d sea e n Amer can Samoa and P fken (1945 reported one ca e n a h te sold er who had been on duty for over a year on var ous South Pac fi I lands Rac al mmun ty f t ex sts ould appear to play a role secondary to unhyg en c env ronmental condit ons in tl e d em nat on of framboes a.

GEOGRAPHIC DISTRIBUTION

Framboes a is w dely though unevenly d str buted throughout the trop al reg ons of the orl l part cularly n areas w th h gh mean annual temperatures and heavy annual ra n fall W lson and Math s (1930) nd ated that n Ha t there appeared to be a lo er inc dence of nfect on as the alt tu le increa ed al ove °,500 feet Framboes a has frequently been intro duced into subtrop cal and tempe ate count es but has never flour shed there

In tl e Amer can Republ cs and the Br ti l West Ind es framboe a s most prevalent on the West Ind an Islands and the northern coast of South Amer ca There s a h gh nc dence of th s d ease n Ha ti and the Domin can Republ c n the Greater Ant lles and in Tr n dad Grenada Ant gua Guadaloupe Montserrat Sa nt Lu a and other lands n the Le er Ant lles Tl e inc lence s lo n Cuba Puerto I o Mart n que and Barbados Among the Central Amer can Republ c Costa R ca and Panama l ave a fa rly h gh nc den e whereas only few cas s l ave been r ported from Honduras Guatemala N aragua and Mex co In South Ame ca frambo s a is ve y con mon n Br t l Gu ana Venezuela Colomb a and B az l It has been reported from Bol v a Ecuador Paraguay and Peru There are but few accurate figures for the number of ca es occurr ng n these countr es The follow ng is a br ef sum mary of the ava lable stat t al nformat on the major ty of whi h was comp led by the Pan Amer an San tary Bureau

Bol via—N nety e ght cases were reported to the health autl o t es n 1944 and 140 were reported th ough August 194

Bra l—McK nley 1935 stated that framboe a is spread pract ally all over tl e country A aujo (19 8 e t n ated 30 000 cases n a populat on of 1 000 000 to 1,200 000 n t e no h n n s ates of Parahiba and Ceará Uscategu (1930) reported that in the relat ely spar ely nhab ed sect ons along the An azon R er from Bel m Pará to the mouth of the I o Negro only a few ca es were found

Colomb a—Llorente Paz and Ponce (1936) est mated there were 34 000 cases n Chocó 6 000 n Valle 8 000 n Cauca and °° 000 n Nar ño represent ng 90 per cent of the total populat on C e a 1941 s ate l that there we e al o t 80 000 cases along the coastal reg ons of Colom b a

Costa R a—McK nl y (1935 repo ted that ° 000 cases have been recorded in tl e Pac fic Lowlan l

Cuba—Par lo Castelló 1939) noted tl at framboes a occu s only in Or ente Prov nce where 4 1 ca es ha e been reported n over forty n ne years

Dom n can Repub c—Mo s and B gelow (19) ma le a careful analysis of 1 046 cases. Lugo (194° found numerous cases n tl e sugar manufa tur ng sect ons u ually among

Secondary skin lesions begin, according to Goodpasture (1923), with a localization of spirochetes *from the blood* in certain papillae from which points the organisms infect the epidermis where conditions appear to be *more favorable* for their growth. The early macule shows only slight hyperkeratosis with thinning of the epidermis due to edema and enlargement of the papillae. At a later stage keratinization increases, small foci of spongiosis appear, plugging of follicles occurs and there is beginning infiltration of plasma cells and



Fig 117.—Framboesiform lesion (×50.) This section shows marked elongation of pegs necrosis of superficial epidermis and intraepidermal abscesses (From Ash and Spitz Pathology of Tropical Diseases W B Saunders Co By permission of the authors and publisher)

lymphocytes, few organisms are present. The papule represents the nonulcerative transitional stage between the macular and the typical framboesiform lesion. In it cellular infiltration is more marked and there are more organisms present in the epidermis than in the macular lesions. The framboesiform lesions closely resemble the primary lesions but are frequently smaller and are covered with yellow crusts. Removal of the crust reveals a superficial ex

B Secondary stage
1 Macular skin lesions with scaling with or without depigmentation
2 Folliculopapular skin lesions
3 Papular skin lesions
4 Framboesiform skin lesions (button yaws')
5 Joint lesions
6 Bone lesions
7 Plantar and palmar skin lesions nonulcerative type
8 Plantar and palmar skin lesions ulcerative granulomatous type (' crab yaws' or ' clavus)
9 Delayed or late plantar and palmar skin lesions
10 Delayed or late bone lesions

C Tertiary stage
1 Nodular skin lesions
2 Ulcerative skin lesions (gumma)
3 Circinate scaling skin lesions (ringworm yaws)
4 Pigmentary skin changes
5 Gummatous lesions of skin and bone
6 Juxta articular nodules
7 Goundou
8 Gangosa
9 Cardiovascular lesions (doubtful)
10 Neurologic lesions (doubtful)

The histologic picture of the various primary and secondary skin lesions as described by Ash and Spitz (1945) is essentially the same allowing for differences in intensity and duration of the tissue reaction and for anatomic differences at the site of the lesion The primary lesions are granulomatous with edema and hyperplastic changes in the epidermis and enlargement and elongation of the rete pegs In lesions one to two months old the superficial portions of the epidermis are usually necrotic and the lesions are covered by crusts composed of keratin debris leucocytes blood and dried serum Underlying this layer there is often a parakeratotic plaque Hyperkeratosis is always present and scattered epithelial pearls and plugged follicles are common The pegs are elongate and irregular presenting a characteristic interlacing branched appearance There is a marked degree of spongiosis and intracellular edema Small intraepidermal vesicles and abscesses are common especially adjacent to similar foci in the papillae Pigment is usually absent from the epithelium In places the elongated papillae protrude through the epidermis which is thin or absent The upper papillary layer is edematous and hyperemic and the lymphatics are dilated The granulomatous infiltrate present in the lower papillary and subpapillary layers is composed mainly of plasma cells and lymphocytes with scattered polymorphonuclear leucocytes and eosinophiles Small vessels are not involved Spirochetes are numerous in the epidermis especially in the granular and basal layers They are occasionally seen in the crusts but are seldom found in the lower segments of the dermis



Fig 118 —Primary lesion of framboesia on external malleolus.



Fig 119 —Same lesion as shown in Fig 118 one week after treatment with 1 200 000 Oxford Units of penicillin

coriation with clean cut edges. It is lined with granulation tissue which bleeds readily. Plantar and palmar skin lesions also resemble the primary lesion except for their persistence which is probably due to the continuous trauma to which they are subjected and the thickness of the epidermis in these areas.

The histology of the tertiary lesions is not well known except in the case of subcutaneous gummas. These show necrosis of tissue and ulceration of the overlying skin. The necrotic area is surrounded by a zone of epithelioid cells and numerous giant cells. Spirochetes are sometimes found in small numbers in these lesions. The gummas are similar to those of syphilis. The juxta-articular nodules show nonspecific granulomatous processes with central necrosis and a peripheral border of epithelioid cells in which numerous giant cells are scattered. Bone lesions evince periosteal proliferation and dense areas of sclerosis. Osteitis may result in a "sabre shin" or produce deformities of the arms or fingers. In gangosa the nasal cartilages may be completely destroyed. The presence of visceral lesions is debatable. Choisser (1929) reported a series of 700 consecutive autopsies in Haiti. In 10 cases which he considered to be definitely framboesia, 8 had aneurysms of the aorta, 1 a gumma of the brain, and the other a spontaneous cerebral hemorrhage. He was unable to differentiate the pathologic process in these lesions from that of syphilis which is also prevalent in Haiti.

CLINICAL SIGNS AND SYMPTOMS

Framboesia runs a comparatively mild clinical course which may be arbitrarily divided into the same three stages described for the pathologic lesions. It rarely results in death, although some untreated or inadequately treated patients may show marked cachexia. A relatively small proportion of cases may develop large destructive and disfiguring late skin and bone lesions, usually accompanied by secondary bacterial infection.

Incubation Period

The incubation period varies from three to six weeks. Frequently the primary lesion is ushered in with prodromal systemic symptoms, such as vague abdominal discomfort, nocturnal headache, joint pains, and an irregular fever. These symptoms often abate upon the appearance of the initial lesion. As previously stated, the primary lesion occurs most frequently on the feet, particularly the malleoli; less common sites are the legs and knees, especially on the anterior aspect of the lower third of the legs. The head, neck, thighs, upper extremities, and genitals are much less frequently involved. The location of the primary lesions does not appear to influence the course of the disease. Some patients are unable to give a history of a primary lesion. In such cases either the lesion was so small it was overlooked or it did not develop, the disease beginning with secondary lesions. Chambers (19 8) reported that in Jamaica there was an increase in primary lesions during the wet seasons, indicating that environmental conditions are more favorable for the spread of infection at those times.



Fig 118 —Primary lesion of framboesia on external malleolus.



Fig 119 —Same lesion as shown in Fig 118 one week after treatment with 1 200 000 Oxford Units of penicillin

Primary Lesion

At the end of the incubation period the primary lesion appears as a small elevated papule a few millimeters in diameter or as a group of papules It occasionally begins as a tiny macule which may go unnoticed In a few days the lesion enlarges to the size of a small pea and becomes surrounded by an inflammatory areola The epidermis begins to crack open and a yellowish seropurulent fluid exudes from the underlying granulomatous base The papule continues to enlarge daily and may attain a diameter of 2 to 6 cm or more apparently depending upon the size of the pre existing injury After a week the surface becomes covered by a dark crust which oozes serum and bleeds easily The lesion is usually painless It may go through the stage of scab formation and healing in two to four weeks prior to the appearance of the secondary lesions More often as the result of secondary infection it persists with the secondary lesions for weeks months or years Frequently it breaks down to form an ulcer with a granulating base and raised edges As a rule the primary lesion eventually heals leaving a noticeable scar which may endure throughout the life of the patient

Secondary Stage

The secondary stage manifests itself as a generalized eruption from two weeks to three months after the appearance of the primary lesion The average time interval between the two stages is from three to four weeks The variation in time may be the result of a number of factors the number of organisms causing infection repeated inoculations the virulence of the organisms and the extent of trauma at the site of inoculation Transitory prodromal symptoms of fever malaise headache and joint pains are again generally present A slight rise in temperature of one to two degrees Fahrenheit often precedes and accompanies the secondary eruption persisting until after the lesions have begun to recede and fresh ones no longer appear The joint pains are not generally accompanied by heat or swelling

The secondary lesions may be profuse over the face limbs buttocks and trunk Occasionally they may be distributed scantily in one or two places or they may not be present at all They are generally more numerous on the buttocks and thighs In many cases lesions appear at the mucocutaneous borders of the nose mouth anus and vagina and on the scrotum and penis Lopez Rizal and Sellards (1926) reported a modification of secondary lesions in a group of patients living in the mountains of Northern Luzon Philippine Islands The lesions were limited to the mucocutaneous junctures of the mouth nose anus and genitals in approximately 90 per cent of the cases This limitation of distribution of lesions has not been observed in patients residing in the mountainous regions of Haiti or Jamaica Mucocutaneous lesions of the mouth occasionally spread directly to the mucous membrane of the lips

The secondary lesions have the same characteristics as the primary lesions Typically desquamating macular lesions are the first to appear In a few days

elevated papules develop in some of the macular areas. *They increase rapidly* in size, the majority obtaining a diameter of from 2 to 4 cm. Itching occasionally accompanies the lesions. Dried serum and dead *epithelium form a* soft yellow crust. Later the crust may become dark yellow, harden and become friable, assuming a characteristic heaped up *appearance. Lesions around* the mouth and nose frequently remain moist and soft. In the genital, anal and perianal regions some lesions may be *condylomatous and others some*what flattened from pressure and are moist. In all the above locations the lesions are not usually painful, but those on the soles of the feet and the palms



Fig 120



Fig 121

Fig 120.—Papular lesions in the secondary stage of framboesia.
Fig 121.—Same patient as shown in Fig 120 one week after treatment with 1,200,000 *Oxford Units of penicillin*

of the hands may be extremely so. The lack of large amounts of loose subcutaneous connective tissue in these areas results in the development of pressure symptoms. Regional lymphadenopathy frequently occurs. The generalized eruption may persist for months or years, coming out in successive crops in long standing cases. In addition to, and occasionally in the absence of the framboesiform eruption some patients may show *papulofollicular* lesions. These appear early as discrete round or ovoid elevations on the skin *0.5 to 1.5 cm in diameter. At times the framboesiform* lesions are circinate. Fox (1943) mentioned an infrequent early secondary eruption consisting of pinhead sized papules in groups which has been called "keratoid yaws" be

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The secondary lesions have the same characteristics as the primary lesions Typically desquamating macular lesions are the first to appear In a few days

difficult and resembles the locomotion of a crab A week or two later the lesions ulcerate and become slightly less painful These lesions tend to remain longer than other secondary lesions and are less responsive to treatment They may continue to appear for years after other secondary lesions have healed Nonulcerative plantar lesions often develop late in the course of the disease sometimes several years after the first attack

During the secondary stage there may be definite bone involvement The tibiae are most commonly affected then the ulnae radii fibulae tarsals metatarsals metacarpals carpals phalanges of fingers and toes and humeri in descending order of frequency The maxillae, clavicles frontal bone



Fig 124 Fig 125

Fig 124 —Circinate framboesiform lesions of the face
Fig 125 —Same patient as shown in Fig 124 one week after treatment with 600 000 Oxford Units of penicillin

femora sternum scapulae and patellae are more rarely affected Paronychiae with periosteal and bone involvement may occur A fusiform or nodular swelling develops over some part of the bone Pain is usually present and may be felt before there is any palpable swelling Gross bone deformity may develop if treatment is not begun early or if it is inadequate

After reaching a certain stage of development the various types of primary and secondary lesions usually begin to regress in the absence of treatment Healing appears to take place by the process of dehydration Exudation diminishes and the crusts disintegrate The hyperkeratotic epidermis is

cause of its supposed similarity to keratosis pilaris He suggested it more closely resembles lichen scrofulosorum

The plantar and palmar skin lesions ("crab yaws") are a distinctive feature of framboesia They are the counterpart of the characteristic generalized eruption The lesions appear as punctate erosions giving the soles

Fig 122



Fig 123

Fig 122 — Flat moist framboesiform lesions on the genitalia
Fig 123 — Flat moist framboesiform lesions in the perianal region

and palms a moth eaten appearance The affected areas are thicker drier and harder than normal as the result of marked hyperkeratosis and desquamation Fissures frequently accompany the lesions The soles and palms become tender and painful Plantar lesions may be so painful that walking becomes

shed and the skin resumes its normal appearance Increased pigmentation and occasionally depigmentation may persist for months As a rule primary lesions leave scars secondary lesions do not

Tertiary Stage

The majority of framboesia cases do not progress beyond the secondary stage *so far as is known* a few cases do not go beyond the primary stage The tertiary stage develops in a few of the untreated or inadequately treated patients in from one to several years after the initial lesion Sometimes the secondary and tertiary stages merge or the interval between the two may be so



Fig 129—*Late* bone lesions in framboesia accompanied by disfigurement and wasting

long that it is difficult to get a reliable history A variety of lesions have been ascribed to the tertiary stage Ulcerative lesions *on* the legs seem to be most common some of which are of a spreading superficial type and others deep They frequently develop at the site of the primary lesion or in close proximity to it The edges of the superficial ulcers *are* usually raised and serpiginous the edges of the deep ulcers are often undermined *The base of* the ulcer



Fig 1²6



Fig 127

Fig 126 —Ulcerati e pl ntar les on (crab ya s) of frambœsia
Fig 127 —Same patient as sl own in Fig 1²6 one eek after treatn ent with 1 200 000 ord Units of penic ll n

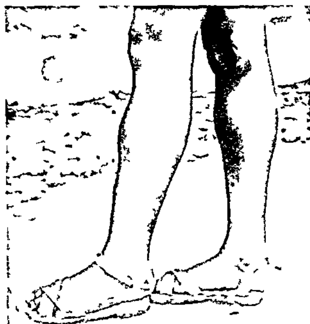


Fig 1²8 —Bowing of t biae due to frambœsia.

Juxta articular nodules occur even less *frequently than gangosa* They appear as firm freely movable painless subcutaneous masses varying in size from 1 to 3 cm They occur most commonly on the extensor aspects of the elbow and knee joints and less frequently over the external malleoli tempero mandibular joints finger joints trochanters and sacrococcygeal joint They *seem to develop in localities which* are most often subjected to pressure and to repeated trauma The lesions persist for years and the skin over them may become attached Suppuration is rare

Goundou is considered to be a rare form of tertiary lesion which like gummas gangosa and juxta articular nodules appears to be most prevalent in areas where treatment facilities are scarce It develops earlier than other tertiary lesions sometimes closely following secondary lesions in young chil *dren It is initiated by exostosis of the frontal process of the maxilla usually* bilateral The lesion may be accompanied by headache and a thin puru lent nasal discharge often tinged with blood As it progresses over a period of months it may involve the nasal and frontal bones producing a large oval tumor The overlying skin is not affected In some cases the nasal passages are obstructed

Some writers feel that framboesia may produce neurologic and cardio *vascular lesions in its late stages Wilson and Mathis (1930) observed 1 493* consecutive cases in Haiti and stated that ptosis blindness and optic neuritis were occasionally encountered No spinal fluid changes have been detected With reference to cardiovascular lesions none have been reported where other causal agents such as syphilis and rheumatic fever have been completely ruled out

DIAGNOSIS

The most important disease to be considered in the differential diagnosis of framboesia is syphilis particularly in the tertiary stages Little aid can be obtained from the laboratory since the etiologic agents are indistinguish able and specific serologic tests are positive in both diseases Spirochetes can readily be demonstrated by dark field microscope examination of serum from primary and secondary framboesia lesions after *removal of the crusts* The Wassermann (complement fixation) Kahn (flocculation) and other specific *serologic tests are positive in over* 99 per cent of patients with early fram boesia The tests become positive two to three weeks after the appearance of the primary lesion The titer increases rapidly and becomes strongly positive during the fifth or sixth week The tests remain positive for months or years occasionally becoming negative in the tertiary stage

DIFFERENTIAL DIAGNOSIS

There are a number of points to be considered in the differential diagnosis of framboesia and syphilis

1 Framboesia is prevalent in many rural areas where syphilis is prac tically unknown while in cities where there may be a great deal of syphilis framboesia is uncommon Wilson (loc cit) observed that in Panama and dif

is generally granulomatous A profuse serous or serosanguineous exudate is present Most ulcers are secondarily infected so that their appearance is altered and a purulent exudate is the rule Healing is slow and may leave disfiguring scars which interfere with function of the affected area particularly around joints

Gummas usually start as small firm subcutaneous nodules After a period of weeks or months the skin over the nodule becomes red and subsequently ulcerates producing a punched out lesion A serosanguineous exudate appears Healing may take place in a few months with extensive scar formation and disfiguration of the skin or the ulcer may become secondarily infected and persist for many months or years Occasionally the gummas are arranged in circles and are spoken of as "ringworm yaws"



Fig 130 —Early gangosa



Fig 131 —Advanced gangosa

Gangosa appears to be initiated by the spread of infection from the upper lip or vestibule of the nose to the mucous membranes of the soft palate or the nasal passages The membrane ulcerates and the process advances destroying soft tissues bone and cartilage The septal cartilage and the structures of the nose are lost leaving a cavernous opening The process may spread to involve the adjacent parts of the upper lip and cheek On occasion it seems to spread to the eyes by way of the nasal ducts Secondary infection probably plays an important role in modifying the appearance of the lesions The incidence of gangosa in areas where framboesia is highly endemic is less than 1 per cent

A number of other skin conditions are to be differentiated from framboesia Some of the more common are as follows

1 **Pyodermas** occur frequently in tropical countries A variety of types of lesions are seen pustules bullae vesicopustules folliculopustules furuncles carbuncles paronychiae and ulcers The principal etiologic agents are staphylococci and streptococci The majority of these can be readily recognized clinically However some become covered with *yellow or honey colored* crusts closely resembling secondary framboesia lesions others ulcerate simulating tertiary framboesia The crusted lesions can be differentiated by dark field microscope examination but the ulcers cannot since it is difficult to demonstrate spirochetes in framboesia ulcers The pyogenic ulcers usually have sharp sloping edges with a foul necrotic base as compared with the *undermined* edges and granulomatous base of the framboesia ulcers However, framboesia ulcers are often secondarily infected so that it is impossible to differentiate them from pyogenic ulcers *Borrelia vincenti* fusiform bacilli and *T refringens* may be found in the ulcers in addition to the pyogenic cocci The so-called tropical ulcers probably fall into this category Differentiation of ulcers is sometimes possible by response to the type of treatment instituted In general pyogenic ulcers will respond to local treatment and framboesia ulcers to specific treatment

2 **Scabies** is frequently seen in the tropics Its characteristic distribution on the webs of the fingers flexor surface of wrists axillae lower part of the abdomen and back and penis and scrotum serves to differentiate it from framboesia Itching is a prominent symptom which is not the case in framboesia Scabies may be complicated by pyogenic *infection or framboesia* making diagnosis more difficult Demonstration of the parasitic mite *Sarcoptes scabiei* by microscopic examination of scrapings from the lesions is not always possible

3 A number of **fungus infections** produce lesions resembling those of *framboesia*

a *Trichophytosis dermatophytosis* or *epidermophytosis* of the hands and feet may be differentiated from framboesia by their limited distribution and the presence of vesicles in the early acute stage of infection Microscopic examination of fungus elements in a potassium hydroxide preparation will *confirm* the diagnosis

b *Tinea versicolor* or *pityriasis versicolor* is characterized by yellow or brown irregularly sized finely scaling macules over the shoulders chest, upper portion of the back axillae and upper part of the abdomen *The etiologic agent Microsporon furfur*, can easily be seen in a potassium hydroxide preparation

c *Onychomycosis* or *"ringworm"* of the nails affects both toenails and fingernails the former more frequently The nail becomes friable thickened deformed and discolored Paronychial inflammation is uncommon The lack of accompanying *skin lesions tends to differentiate* this condition from framboesia

ferent parts of the world where a high incidence of framboesia is found the incidence of syphilis is correspondingly low

2 Framboesia is probably not congenital whereas syphilis definitely is giving rise to Hutchinsonian teeth bossing of the frontal bones iritis interstitial keratitis etc Framboesia does not cause abortion in pregnant women and children born to infected mothers do not show lesions or positive serologic tests

3 The primary lesion of framboesia is usually extragenital In syphilis the initial lesion is on the genital organs in a majority of the cases

4 The primary lesion of syphilis is often indurated and is not usually covered with a friable crust thereby differing from framboesia

5 Regional lymphadenopathy is generally more marked in framboesia than in syphilis and the glands are less firm and nodular

6 A history of the primary lesion and evidence of its presence in the form of a scar are more often obtainable in framboesia than in syphilis

7 The characteristic secondary lesions in framboesia covered with heaped up friable yellow crusts have not been observed in syphilis

8 Mucous membrane lesions are common in syphilis but not in framboesia except when direct spread from a cutaneous border is evident

9 The typical painful scrub yaws lesions on the soles of the feet and the palms of the hands in framboesia apparently do not occur in syphilis

10 Alopecia is sometimes seen in syphilis but has not been reported in framboesia

11 Gangosa and goundou occasionally develop in the late stages of framboesia but not in syphilis

12 Visceral lesions do not appear to develop in framboesia whereas they are not uncommon in syphilis In this category fall such lesions as gummas of the liver testes and kidneys neurologic involvement including meningitis hemiplegia arteriosclerosis tabes dorsalis and general paralysis and cardiovascular lesions such as aortitis myocarditis and aneurysm

13 Spinal fluid changes are a feature of syphilis but not of framboesia Spinal fluid Wassermann and Kahn tests are negative in cases of framboesia

14 A reciprocal immunity seems to exist between framboesia and syphilis. Schobl and Miyao (1929) and Schobl (1930) showed that a high degree of immunity to framboesia protected Philippine monkeys against cutaneous infection with syphilis and vice versa In human experiments Turner (1936) reported unsuccessful attempts to infect ten patients with latent syphilis by inoculation of *T pertenue* With regard to experimental infection of framboesia patients with syphilis only one instance is reported in the literature (Charlouis 1881) It seems likely that in such instances insufficient time had elapsed for the development of immunity

15 There is considerable experimental evidence that *T pallidum* possesses pathogenic properties in rabbits which differ from those of *T pertenue* and these may in part explain the differences between framboesia and syphilis in man (Pearce and Brown 1925 Turner and Chesney, 1934)

nosis of framboesia Definitive diagnosis of leishmaniasis depends upon the demonstration of *Leishmania tropica* in smears or cultures made from the lesions

5 **Mucocutaneous leishmaniasis** ("espundia") is widely distributed throughout Central and South America Ulceration about the margins of the nose and mouth may resemble gangosa Here again definitive diagnosis of leishmaniasis depends upon the demonstration of the etiologic agent *Leishmania braziliensis* in smears or cultures made from the lesions This is difficult in advanced cases with extensive secondary infection

6 **Seborrhea or seborrheic dermatitis** may be confused with the macular scaling lesions of the secondary stage of framboesia Its distribution characteristically corresponds to the areas of sebaceous gland concentration that is scalp mid portion of the face and presternal and interscapular regions Mild to severe dermatitis may occur in the intertriginous areas of the axillae umbilicus crural folds and gluteal cleft In questionable cases the demonstration of spirochetes on dark field microscope examination will establish the diagnosis of framboesia

7 **Pityriasis rosea** is a common papulosquamous eruption which may resemble the early secondary stages of framboesia Its distribution is typically over the back chest abdomen arms and thighs The lesions tend to be arranged with the long axis along the lines of cleavage They do not go through the course of development characteristic of framboesia lesions

8 **Lichen planus** may simulate some of the papular lesions of the secondary stage of framboesia The lesions frequently appear on the wrists forearms buccal mucosa and genitals They are generally violaceous flat topped and angular Itching is usually severe Here again the lesions do not go through the course of development characteristic of framboesia

9 **Psoriasis** may occasionally produce framboesiform lesions The typical psoriatic papule or plaque has a dull red base which is covered with a silvery moderately adherent scale The distribution is characteristically on extensor surfaces It is extremely chronic and like the secondary stage of framboesia does not usually leave scars Removal of the crust reveals a shiny red surface which is unlike the granulomatous base of the framboesiform lesions

10 **Acne vulgaris** in the papular and pustular stages may be confused with the secondary stage of framboesia The lesions are typically located on the forehead cheeks chin upper chest shoulders and upper portion of the back It is common in adolescents The lack of evidence of a primary lesion and the duration of lesions serve to differentiate this disease from framboesia

11 **Lupus vulgaris** is a form of tuberculosis of the skin which may simulate secondary and tertiary framboesia It is characterized by plaques of small soft applebutter like" tubercles Satellite nodules develop and then coalesce to form irregular groups of various sizes The face particularly the nose is most frequently involved The course is slow but progressive The lesions generally break down and form small crusted ulcers which are ultimately replaced by fibrous tissue The scarring is usually thicker and firmer

d *Tinea cruris* or "*ringworm*" of the groin ("dhobie itch") involves the upper inner surfaces of the thighs the inguinal folds and occasionally the scrotum buttocks intergluteal folds umbilicus and axillae The lesions appear as well marginated reddish patches with a slightly scaling surface They often tend to clear in the center with a papular or finely vesicular scaling border The localization and appearance of these lesions is generally sufficient to establish the diagnosis

e *Tinea corporis* or *ringworm'* of the body may appear in the form of circinate and annular red scaling lesions with an inflammatory reaction and active vesicular borders or as large irregular plaque like lesions with sharp borders and no vesiculation Fungus elements can usually be demonstrated in potassium hydroxide preparations

f *Tinea barbae* or *ringworm* of the face is a pustular folliculitis with induration and sometimes canalization The hairs of the bearded region become loose and are easily removed The presence of fungus elements in potassium hydroxide preparations establishes the diagnosis

g *Blastomycosis* is a more serious fungus infection occurring in North and South America which may have both cutaneous and systemic manifestations The skin lesions usually occur on the face neck hands wrists arms feet or legs They start as papules or pustules which develop into chronic ulcers There is usually little pain tenderness systemic reaction or regional lymphadenitis Diagnosis can be made only by demonstrating the characteristic budding organisms *Blastomyces dermatitidis* or *B brasiliensis* in pus from the lesions or in histologic sections

h *Sporotrichosis* is a chronic granulomatous fungus infection producing gumma like skin nodules ulcers and abscesses Diagnosis is based upon the cultural characteristics of the etiologic agent *Sporotrichum schenckii* after inoculation of infected material on Sabouraud s medium and inoculation into laboratory animals (rats mice and guinea pigs)

i *Actinomycosis* is a chronic suppurating granulomatous fungus infection of the skin characterized by multiple abscesses and fistula formation It is most frequently seen about the face and neck (lumpy jaw) The characteristic yellow granules of *Actinomyces bovis* can be readily demonstrated in the pus from the lesions by microscopic examination

j *Maduromycosis* or *Madura foot* is a chronic granulomatous fungus infection usually limited to the lower extremities producing extensive destruction of the soft tissues and the bony structures particularly of the feet In advanced cases the foot becomes a mass of cyst like areas with intercommunicating sinus tracts and multiple externally draining sinuses The characteristic granules of *Actinomyces* and branching mycelia of *Nocardia* and *Monosporium* can be demonstrated in potassium hydroxide preparations of pus

4 **Cutaneous leishmaniasis** (Oriental sore forest yaws ') occurs in many areas where framboesia is endemic Ulcers develop on the legs and arms which may closely resemble the primary lesion of framboesia The subsequent development of widespread secondary lesions establishes the diag

Arsphenamine (Salvarsan)

The chemical base is 3,3′ diamino 4,4′ dihydroxyarsenobenzene, marketed as the dihydrochloride salt containing about 31 per cent arsenic in the trivalent form. It is given intravenously in doses equivalent to 0.010 Gm per kilogram of body weight. The average single therapeutic dose is 0.40 Gm for men and 0.30 Gm for women. The drug is prepared by dissolving the powder in fresh sterile distilled water 10 c.c. for each 0.1 Gm of acid arsphenamine. The solution must then be made alkaline by the addition of 0.85 c.c. of a normal (4 per cent) solution of sodium hydroxide for each 0.1 Gm of acid arsphenamine. After alkalinization is complete the solution is filtered through sterile gauze and an additional amount of water is added to make a final volume of 20 c.c. of solution for each 0.1 Gm of arsphenamine. It must be allowed to stand for thirty minutes before being used. Solutions should not be allowed to stand more than four hours before use. Injection must be given slowly by gravity. Three to six injections at weekly intervals are generally given. It is important that the patient eat lightly on the day of injection and omit the meal following the injection.

A number of systemic reactions may follow the use of arsphenamine. The intravenous injection of 0.2 Gm or more of unalkalinized acid arsphenamine almost always results in sudden death.

The Jarisch Herxheimer reaction (therapeutic shock) occurs only after the first and not after subsequent injections of arsphenamine. Within a few hours after the drug is given there occurs a chill, a rise in temperature reaching 103° to 104° F, general malaise and aching. The serious focal reactions characteristic of late syphilis have not been reported.

Several reactions following the injection of arsenicals are nonspecific and are due to the use of the intravenous route. Among these are the "tubing" reaction, the "ether" odor and gastrointestinal reactions. The "tubing" reaction is caused by improper preparation of new rubber tubing. It most often consists of fever, vomiting and headache. The "ether" odor occurs only after the use of arsphenamine, neoarsphenamine and Mapharsen. The odor, which is like that of ether or garlic, is due to the presence of the drug in the blood of the nasal mucosa and occurs within a few seconds after the injection. The patient's awareness of the odor may be lessened by having him breathe through the mouth. The gastrointestinal disturbances comprise the most frequent type of reaction after the arsphenamines. Nausea, vomiting, diarrhea, headache and malaise develop within four to twelve hours after treatment and usually last a few hours. These disturbances develop less frequently if patients are cautioned to eat lightly on the day of treatment and to omit the meal following treatment.

Angioneurotic symptoms may develop after the administration of the arsphenamines. The most common of these is the *nitritoid crisis*. The conjunctiva becomes suffused, the patient complains of being hot, of a feeling of oppression in the chest and palpitation. If the injection is not stopped the patient goes into shock with flushing of the skin, cough, vomiting and

than that of framboesia ulcers unless the latter were secondarily infected A history of contact with other cases of tuberculosis may be obtained Definitive diagnosis of lupus vulgaris can be established by biopsy examination and guinea pig inoculation

12 **Scrofuloderma** is a form of tuberculosis in which the skin is involved secondarily by direct extension from lymph nodes or bones The cervical lymph nodes are those most commonly affected becoming enlarged firm and adherent to the overlying skin Over a period of months or years the overlying skin becomes thinned purplish and depressed It then sloughs at one or more points to form ulcers which serve as mouths of sinuses. These extend deep into the diseased tissue and discharge purulent material At this stage the lesion may resemble a framboesia gumma which has broken down Constitutional symptoms are generally slight or lacking The lesions may persist for a year with little or no change occasionally they heal spontaneously with the formation of rough corded cicatrices The initial lymph node involvement is an important clinical point in differentiating this disease from framboesia Laboratory diagnosis can be made by biopsy examination and guinea pig inoculation

13 **Leprosy** in its early and late stages may simulate framboesia The macules of leprosy are usually oval bilateral in distribution and extend peripherally being most common on the lobes of the ears alae nasae forehead eyebrows cheeks and chin Sensory changes generally develop and serve to differentiate these lesions from those of framboesia The subsequent appearance of nodules with induration and thickening of the skin results in the characteristic leonine facies of leprosy The nodules frequently ulcerate Neural involvement results in trophic changes in the skin Atrophy of muscles leads to contractures and deformities with resorption of bone and ulceration of the skin The diagnosis of leprosy can generally be made on clinical grounds Definitive diagnosis is based upon demonstration of the etiologic agent *Mycobacterium leprae* in the skin

TREATMENT

A number of organic arsenical drugs bismuth and penicillin are specific in the treatment of yaws Mercury and potassium iodide separately or combined tartar emetic and carbarsone are considered to be less satisfactory therapeutic agents

Strong (1910) first tried arsphenamine (Salvarsan) in the treatment of human framboesia and reported its marked specificity It has frequently been observed that one injection of an arsenical drug bismuth or penicillin resulted in rapid healing of the primary and secondary lesions of framboesia This has led to the assumption that this disease is easy to cure However in those few instances where adequate post treatment clinical and serologic observations have been made it has been found that the majority of these patients relapsed frequently and never attained seronegativity

Pertinent information concerning the use of some of the above mentioned drugs in the treatment of framboesia is given below

incidence is highest following neoarsphenamine and seldom if ever occurs after Mapharsen Jaundice appears at variable intervals after treatment ranging from a day to many months It closely resembles infectious hepatitis that is a day or two of malaise slight fever generalized aching epigastric distress anorexia nausea and occasional vomiting followed in four to eight days by the appearance of rapidly deepening jaundice of the *obstructive type* As the jaundice develops the symptoms often disappear The liver becomes enlarged and slightly tender Bile appears in the urine and disappears from the stools Rarely there develop signs and symptoms of acute yellow atrophy intractable vomiting mental dullness apathy drowsiness coma convulsions and death within seven to fourteen days The mechanism of postarsphenamine jaundice is uncertain possibly being due to the direct toxic effect of the arsenicals on the liver Treatment is symptomatic Daily intravenous injections of calcium gluconate (10 c c of 10 per cent solution) appear to accelerate symptomatic improvement

Neoarsphenamine (Neosalvarsan)

Neoarsphenamine (Neosalvarsan) is sodium 3 3′ diamino-4 4′ dihydroxy arsenobenzene N methanol sulfoxylate a derivative of arsphenamine containing 19 to 22 per cent of arsenic in the trivalent form It is given intravenously *in doses equivalent to 0 015 Gm per kilogram of body weight The average* single therapeutic dose is 0 75 to 0 9 Gm for men and 0 6 to 0 75 Gm for women The drug is prepared by dissolving the powder in fresh distilled water using from 2 to 10 c c per 0 1 Gm of drugs A total volume of 15 to 20 c c is usually employed for the average treatment It is not necessary to alkalinize the solution as must be done when preparing arsphenamine The drug must not be allowed to stand longer than twenty minutes Injection is made slowly by syringe at the rate of not more than 0 1 Gm per 30 seconds As in the case of arsphenamine three to six injections at weekly intervals are generally given

Solutions of neoarsphenamine are considerably easier to prepare and administer than those of arsphenamine It causes fewer gastrointestinal reactions is less irritant when accidentally injected into tissues and does not thrombose veins Its chief disadvantage is its instability The ampules must be kept in the dark and on ice if possible and must not be over six months old

Sulfarsphenamine

Sulfarsphenamine is disodium 3 3′ diamino 4 4 dihydroxyarsenobenzene N dimethylenesulfonate a formaldehyde sulfoxylate derivative of arsphenamine containing 19 per cent of trivalent arsenic It is administered intramuscularly in doses equivalent to 0 010 to 0 025 Gm per kilogram of body weight The average single therapeutic dose is 0 6 Gm for men and 0 4 Gm for women The drug is prepared by adding fresh distilled water to the ampule 0 3 c c per 0 1 Gm of drug Solution should occur quickly and com

severe back pain Occasionally there develops swelling of the face, lips, tongue, or eyelids, and generalized urticaria The patient experiences fear of impending death, and the reaction may sometimes be fatal However, the symptoms usually disappear in twenty to sixty minutes without residual effects and even without treatment It is safer to treat the patient by intramuscular injection of 0 5 to 1 0 c c of a 0 1 per cent epinephrine hydrochloride solution The incidence of this reaction is about 0 1 per cent of all injections of arsphenamine and neoarsphenamine but has not been reported after Mapharsen The cause is not known Rapid injection is undoubtedly the major factor in most cases

Acute heart failure may result when an arsphenamine is administered to a patient with myocardial damage from cardiovascular syphilis Thus, heart disease of any nature is a contraindication to the use of the arsphenamines

The arsphenamines are capable of producing a wide variety of toxic manifestations in the skin ranging from minor dermatitides to grave and sometimes fatal exfoliative dermatitis The distribution may be widespread or localized as in the case of herpetiform and fixed arsenical lesions The major dermatitides are due to drug sensitization and nearly always necessitate abandonment of arsenical treatment The interval between treatment and the appearance of the rash is about five days on the average It begins usually as a maculopapular or vesicular dermatitis, often limited at first to the extremities, but rapidly spreading over the whole body Erythema may be generalized and itching is severe In the milder cases the process may stop here, and the eruption disappears in a few days In the more severe cases, marked scaling and exfoliation occurs and the skin of the entire body is desquamated in large flakes Marked constitutional symptoms and evidence of visceral damage may be associated with the eruption Fever, malaise, and prostration are common, jaundice albuminuria hematuria, and polyneuritis are relatively infrequent complications The patient should be hospitalized and treated symptomatically Intravenous glucose (500 c c of 5 per cent solution) and calcium gluconate (10 c c of 10 per cent solution) should be given daily Large amounts of vitamin C (0 500 Gm) daily may be beneficial The incidence of the dermatitides varies from 0 5 to 14 per cent of all injections of arsphenamines being highest following sulfarsphenamine and lowest after Mapharsen injections

Among the reactions from arsphenamines in the central nervous system are polyneuritis hemorrhagic encephalitis transverse myelitis, and ocular damage These occur infrequently and usually only after a large number of injections have been made

Blood dyscrasias due to the arsenical drugs are relatively rare Three types of reaction are recognized thrombocytopenia, granulocytopenia, and aplastic anemia These are among the most serious of arsenical treatment complications, having a high mortality rate

Postarsphenamine jaundice is a fairly frequent complication of arsphenamine therapy, occurring in approximately 0 02 per cent of all injections The

week's rest the course of treatment is repeated. Its chief advantage is that it can be given orally, but this is outweighed by its toxicity and the poor results obtained with it. The full course of treatment with acetarsone may be more expensive than that of neoarsphenamine or Mapharsen.

Bismuth

Bismuth is available in a confusing number of preparations. The metallic bismuth content of these varies so that it is necessary to acquaint oneself with the preparation being used. Some of those commonly used are as follows:

a. **Bismuth subsalicylate** is an insoluble preparation made up of a 10 per cent suspension of basic bismuth salicylate in olive or peanut oil. It contains *0.057 Gm. of metallic bismuth per cubic centimeter of drug solution.* *Three* to six intramuscular injections of 1 or 2 c.c. (0.1 or 0.2 Gm.) at weekly intervals are recommended.

b. **Potassium bismuth tartrate** is another insoluble preparation made up of a 10 per cent suspension of basic bismuth potassium bismuthotartrate in peanut oil with 0.4 per cent of butyn. The dosage is the same as that of bismuth subsalicylate.

c. **Bismosol** is a soluble preparation of potassium sodium bismuthotartrate in 10 per cent glucose solution. It contains 0.035 Gm. of metallic bismuth per cubic centimeter of solution. It is administered intramuscularly twice or three times weekly for two or three weeks in doses of 1 c.c. (0.1 Gm.) each.

d. ***Thio-bismol*** *is another soluble preparation of sodium bismuth thioglycollate.* 0.2 Gm. is dissolved in 1 c.c. of distilled water. It contains 0.076 Gm. of metallic bismuth per cubic centimeter of solution. The dosage is the same as that of bismosol.

Toxic effects occur rarely if an acceptable bismuth compound is given properly by the intramuscular route. Injection of 1 c.c. of air into the muscle before withdrawing the needle and routine massage are two ways of decreasing the discomfort attending treatment. Large numbers of injections of insoluble bismuth have been given with no untoward local effect. Sterile abscesses and sclerosing myositis are seen infrequently. The accidental injection of bismuth into a vein may cause oil embolism of the lungs which may be fatal. Arterial embolism results in painful induration of the buttock. The insertion of the needle before syringe is attached and retraction of the plunger for several seconds to see whether blood can be aspirated are precautions to be taken in order to prevent accidents.

Certain systemic reactions may occur following the administration of bismuth. Pigmentation of the gum margins and buccal mucosa is frequently seen after six or more injections. It persists for years but has no serious significance. Ulcerative stomatitis calls for immediate cessation of bismuth therapy. Jaundice, nephritis and dermatitis are uncommon. At times gastrointestinal disturbances, malaise, fever, headache and pains in the joints and bones develop after each injection and may be serious enough to necessitate cessation of the drug.

pletely Solutions should not be permitted to stand more than three or four hours Here again three to six injections at weekly intervals are generally given

Sulfarsphenamine is the only arsphenamine well tolerated by intramuscular injection It is most useful in the treatment of infants and children as well as in some obese patients and others with inaccessible veins It is stable in solution and in the ampule Immediate reactions are less common than with the other arsenicals but the incidence of serious late reactions in adults is so high that sulfarsphenamine should not be employed if it is possible to use one of the other arsenicals intravenously Fortunately infants appear to be less susceptible to the untoward effects of the drug and for them it is probably the drug of choice at present

Mapharsen (Mapharside)

Mapharsen (Arsenoxide) is 3 amino 4 hydroxyphenylarsinoxide hydrochloride representing a partial oxidation product of arsphenamine It contains 29 per cent of trivalent arsenic It is administered intravenously in doses equivalent to 0 0010 Gm per kilogram of body weight which is one tenth that of arsphenamine The average single therapeutic dose is 0 06 Gm for men and 0 04 Gm for women The drug is prepared by dissolving the powder in fresh sterile distilled water using 2 to 3 c c per 0 01 Gm of drug Solution occurs quickly with effervescence Stirring to insure solution is permissible and desirable Aeration and exposure for hours does not increase the toxicity or decrease the therapeutic value of the solution A brown color may appear after prolonged standing but this is of no importance Injection is made rapidly by syringe giving the entire dose within fifteen to thirty seconds This lessens pain in the arm and decreases the possibility of thrombosis from vascular irritation Three to six injections at weekly intervals are usually given

Mapharsen has a number of advantages over the arsphenamines It is easy to administer requiring no special precautions in preparation It can be given by syringe and can be injected rapidly as soon as the solution is made Large amounts of solution may be prepared for mass treatment in the clinic because the solution keeps for hours It is a pure chemical substance which is uniform in constitution and can be chemically as well as biologically standardized The dose of Mapharsen is much smaller than that for arsphenamines so that less arsenic need be handled by the body Gastrointestinal upsets dermatitides and visceral reactions are less frequent Nitritoid reactions do not occur Excretion appears to be more rapid than that of the arsphenamines so that Mapharsen can be given twice weekly for two or three weeks

Acetarsone (Stovarsol)

Acetarsone (Stovarsol) is acetylamino hydroxyphenylarsonic acid It is a synthetic pentavalent arsenical which may be administered by mouth The drug is supplied in tablets containing 0 05 0 25 and 0 1 Gm The dose for adults is 0 25 Gm three times daily for seven days After a

With regard to the effect of treatment on the blood only a few extensive studies have been reported Goodpasture and de Leon (1923) found that the Wassermann test which was strongly positive before treatment gradually weakened and became negative in seven cases within six months after treatment Chambers saw reduction of seropositivity Dwinelle Rein Sternberg and Sheldon reported that approximately 98 per cent of the patients who had received 1 200 000 units of penicillin in aqueous solution over a four day period showed definite evidence of reduction in Kahn titer three months after treatment

PROPHYLAXIS AND CONTROL

The avoidance of direct and indirect contact with an infectious case of framboesia is an obvious preventive measure Isolation and treatment of such cases should be carried out if possible Infected children should not be allowed to attend school When feasible the lesions should be covered with a clean dressing The wearing of shoes stockings and trousers will prevent trauma of the skin of the extremities Cuts or abrasions may be treated locally with mercury ointment The liberal use of soap and water is an important prophylactic weapon but this is usually beyond the economic and physical means of natives in highly endemic countries Mass treatments regularly and continuously in these areas appear to be the only approach to control To be successful adequate organization health education sufficient funds and trained personnel are needed The development of a satisfactory one treatment drug would be a valuable contribution Penicillin in oil beeswax or a similar preparation holds promise in this respect

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The insoluble bismuth preparations appear to hold preference over the soluble preparations in the treatment of framboesia Bismuth is easier and more economical to administer than the arsphenamines and is safer for aged and weak patients It may be used to advantage in combination with the arsphenamines or Mapharsen

Penicillin

Penicillin is the most recent addition to the specific therapy of framboesia It may be administered intravenously or intramuscularly The dosage has not been definitely established but it seems likely that it should approach that employed at present for syphilis namely 2 400 000 Oxford Units or more However there are reports in the literature of the use of as little as 10 000 U Dwinelle Rein Sternberg and Sheldon (1946) treated 500 patients in Haiti with total doses of 1 200 000 Oxford Units for adults The patients were divided into three approximately equal groups One group was hospitalized and each patient regardless of age was given thirty intramuscular injections of 40 000 Oxford Units of penicillin sodium in aqueous solution every three hours day and night The second group was treated on a two day ambulatory basis in a clinic Each adult patient received two injections of 600 000 Oxford Units of penicillin calcium in peanut oil with 4 8 per cent beeswax by weight (300 000 U per cubic centimeter) twenty four hours apart The dosage in this and the subsequent group was graded down for children those 6 to 12 years of age received a total of 600 000 Oxford Units and those 13 to 16 years received a total of 900 000 U The last group was treated on a one day *ambulatory basis the adults receiving two injections of 600 000 Oxford Units* of penicillin calcium in peanut oil with beeswax ten to twelve hours apart No severe toxic reactions were encountered Approximately one half of the hospitalized patients were observed to have a rise in temperature of 100° to 104° F two to eight hours after treatment was started All temperatures gradually returned to normal in ten to twelve hours

The response of framboesia lesions to regular arsphenamine Mapharsen bismuth or penicillin therapy is rapid and remarkable Healing of most primary and secondary skin lesions is usually complete within a week unless extensive secondary bacterial infection is present Bone lesions heal readily if treated early Crab lesions and tertiary stage ulcers respond slowly to treatment Gangosa and goundou may be arrested only temporarily showing little or no improvement

Infectious relapsing lesions occur more frequently during the first year following treatment than in the second year Chambers (1938) reported that the percentage of relapses of cases receiving four or more treatments was less than of cases receiving three or less whether treatment was with neoarsphenamine or with bismuth salicylate Figures for the incidence of relapses after Mapharsen therapy are not available at present A large number of patients have been treated with Mapharsen in Haiti with excellent clinical results Dwinelle Rein Sternberg and Sheldon (1946) reported a relapse rate of less than 1 per cent within six months after treatment with penicillin

CHAPTER 17

THE VIRUSES AND VIRUS DISEASES OF MAN—GENERAL CONSIDERATIONS

S EDWARD SULKIN

The study of viruses has grown during the last thirty years from an obscure and little known subject into an important branch of medical science. Although viruses have been known to exist for more than half a century their small size has precluded truly scientific study until recent years when viruses and the diseases due to them have been studied extensively. When viruses first became known a tendency arose to assign viral etiology to any disease the causal agent of which was in question but during the past two decades the subject has developed precision and the list of known virus diseases has begun to be differentiated. Advances have been so rapid and contributions to our knowledge so varied and numerous that only the major discoveries can be considered in this discussion.

The virus diseases which are encountered in practically all specialties within the field of medicine vary in their clinical and epidemiologic manifestations in the same manner as bacterial infections. Certain viruses cause disease of the central nervous system, others affect the eye while still others may produce cutaneous lesions. The respiratory diseases caused by viruses are among the most common ailments and numerous tropical diseases fall within this category.

THE NATURE OF VIRUSES

Much of the information concerning the nature of viruses has been obtained through the use of high speed analytical centrifuges by x ray analysis by filtration through graded collodion membranes and through the use of electron microscopy. Measurements of the tobacco mosaic virus have been made possible through the discovery of a method of separating the virus in purified and crystalline form. The tobacco mosaic virus has now been studied extensively and provides a standard scale of size by which all viruses are measured. The particle size of many of the large viruses such as those of psittacosis and trachoma has been determined by direct visual observation while those too small to be resolved with ordinary light have been measured by photography with ultraviolet light or with the electron microscope. The molecules of tobacco mosaic virus as revealed by the electron microscope appear as pencil like structures while those of the virus of equine encephalo*myelitis seem to be circular in shape and uniform in size.* Electron microscope studies of the elementary bodies of the vaccinia virus reveal rectangular particles of uniform size in which can be seen areas of concentration somewhat darker than the surrounding material.

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droplet infection the virus reaching the central nervous system from the nasal mucosa by traveling along the olfactory nerve Recent studies of the pathogenesis and pathology of poliomyelitis however would indicate that portals of entry other than the nasopharynx exist in the human disease Lesions in the olfactory bulbs which occur when the disease is produced experimentally in the monkey by instilling the virus into the nose are uncommon in human poliomyelitis Evidence suggests that the alimentary tract is the usual portal of entry of the virus Supporting this view are the observations concerning the persistence of virus in stools of convalescents presence of virus in stools of healthy contacts and spread of the disease by healthy carriers and by flies Whatever the portal of entry virus may be recovered from the intestinal tract more easily than from the nasopharynx

Numerous studies have been undertaken to determine the mode of transmission of the virus encephalitides Several investigators suggested the possibility of mosquito transmission in St Louis encephalitis and the experimental transmission of the Western equine virus with *Aedes aegypti* (Kelser 1933) indicated a similar mode of spread in equine encephalomyelitis Studies conducted at the Hooper Foundation of the University of California (Hammon and Reeves 1945 Howitt and van Herick 1942) have shown that both of these viruses are endemic in certain areas and that the sera of many mammals and birds contain neutralizing antibodies to these viruses Hammon et al (1942) isolated several strains of the St Louis virus and the Western equine virus from a single species of mosquito (*Culex tarsalis* Coquillet) and found that this mosquito was capable of transmitting these viruses under experimental conditions (Hammon et al 1942a) Other species of mosquitoes have subsequently been added to the list of possible vectors (Hammon Reeves and Gray 1943) It is possible that arthropods other than the mosquito might be capable of transmitting these diseases Supporting this idea is the observation by Blattner and Heys (1943) that experimentally infected dog ticks (*Dermacentor variabilis* Say) are capable of transmitting the disease Smith Blattner and Heys (1944) also reported isolation of St Louis encephalitis virus from chicken mites (*Dermanyssus gallinae)* and showed that mites infected in nature retained the virus after five months of propagation in the laboratory Congenital transfer of the virus from the adult female through the egg into the first stage nymph could be affected (Smith Blattner and Heys 1945)

In 1948 Smith et al presented a concept of the epidemiology of St Louis encephalitis based on well documented experimental evidence They suggest that two blood sucking vectors may be involved one an arachnid the mite which maintains the virus in nature by transovarian passage the other an insect the mosquito which carries the virus from birds to other vertebrates including man Because of the similarity in the natural history of equine encephalomyelitis to that of St Louis encephalitis it is likely that the same factors might be involved in the epidemiology of equine encephalomyelitis This concept is supported by the fact that the Western equine virus was isolated from chicken mites *Dermanyssus gallinae,* in nature by the author during the course

Many of the early workers regarded viruses as minute microbes which simply could not be resolved by means of ordinary light. These agents possess the ability to multiply when introduced into living cells. In fact there is direct microscopic evidence that at least some of the larger viruses (e.g. elementary bodies of vaccinia) multiply by binary fission just as do bacteria. The ability to proliferate and become adapted to changes in environmental conditions is a property of the living organism distinguishing it from inanimate matter. For this reason Green (1935) suggested that viruses might be regarded as bacteria which have lost certain enzyme systems and being obligate parasites are dependent on the metabolism of the host cell for specialized functions other than reproduction. Some workers on the other hand have suggested that they might be nonliving autocatalytic enzyme-like agents since they cannot be cultivated apart from living cells. Supporting this view was the report by Stanley (1935) of the successful isolation of a crystalline protein possessing the properties of the tobacco mosaic virus. No conclusion can as yet be drawn regarding the true nature of the viruses though the observations of Stanley have given new impetus to this field of investigation.

Certain species of microorganisms (e.g. Salmonella group) have been found to contain seven or eight separate antigens which make up the antigenic mosaic of the cell. A similar situation obtains with many viruses and the antigenic complexity may be indicated by the antibodies produced. In many instances one type of antibody is elicited by the virus and the other is produced by the soluble antigen which is separable from the virus. The virus apparently gives rise to the so-called neutralizing antibodies while the soluble antigens produce antibodies which can be demonstrated by the classical precipitation, agglutination or complement fixation tests. Not long ago Smadel, Ward and Rivers (1940) found that the soluble antigen of infectious myxoma of rabbits contained two immunologically distinct components which could be separated by certain physical methods. Vaccinia virus has been shown to have at least five antibodies demonstrable in animals which recover from infection with this agent (Smadel and Hoagland 1942). Other viruses appear to be more simple; for example in poliomyelitis the only humoral antibody which can be demonstrated is one which neutralizes the virus, and tobacco mosaic and rabbit papilloma produce complement fixing and neutralizing antibodies which react with a single antigen.

EPIDEMIOLOGY

Much information has been accumulating concerning our understanding of the mode of transmission of certain diseases of viral origin. But the problem is far from solved at this time. For example the true epidemiology of poliomyelitis is not yet clearly understood. It appears certain that many factors involving environmental temperature, presence of insects and possibility of an extrahuman reservoir of the virus must be considered. For many years it was thought that poliomyelitis was a contact disease spread by

The epidemiology of many of the other virus diseases is equally perplexing. One of the greatest mysteries of epidemiology is what happens to a virus between epidemics and what causes it to reappear from its quiescent state. An important step toward the solution of this problem was made by Shope (1943) when he noted that swine lungworms (*Metastrongylus elongatus* and *Choerostrongylus pudendotectus*) nematodes parasitic in the bronchioles of the lungs of swine were capable of harboring swine influenza virus and of transmitting it from animal to animal. Complicating this apparently simple mode of transmission is the fact that the lungworm has an intermediate host of its own. Fig. 132 indicates diagrammatically the life cycle of the swine lungworm and represents the author's interpretation of Shope's studies concerning the swine lungworm as a reservoir and intermediate host for swine influenza virus. The virus apparently persists in the lungworm in a noninfective form from which it can be provoked into activity by appropriate stimuli (intramuscular injections of *Hemophilus influenzae suis*). The fact that noninfective virus is able to survive for at least two years in the lungworm larvae in the earthworm and, in addition, for several months in the swine respiratory tract would explain survival of the virus between epidemics. Furthermore Shope (1943) observed that transmission of swine influenza virus by lungworms takes place only if experiments are conducted during the fall and winter months, which fits well with the seasonal incidence of swine influenza. What causes fully active swine influenza virus to become noninfective when taken up by the lungworm *and to resume its infectivity when it again finds itself* within a susceptible host is still unknown. These observations, probably the most important in the field of virology in recent years, suggest that a similar cycle might operate in many virus diseases of the human being. In recent studies Syverton et al. (1947) showed that the parasitic nematode *Trichinella spiralis* can serve as a vehicle for the experimental transmission of lymphocytic choriomeningitis virus from one host to the next. These observations may have practical implication in the epidemiology of human lymphocytic choriomeningitis.

DIAGNOSIS

The diagnosis of certain diseases of viral origin may be confused by their frequent association with other infectious processes of similar clinical manifestations. For example, influenza during the acute phase may be accompanied by infectious "colds," and later may be complicated by pneumonia or central nervous system involvement. Also encephalitis may complicate such diseases as smallpox, measles, mumps, chicken pox, and whooping cough. The study of virus diseases is rendered more difficult by the interrelationship of these maladies with other infections, both bacterial and viral. In recent years correlated clinical, laboratory, and epidemiologic studies have permitted investigators to dissociate certain virus diseases which present similar clinical manifestations and to establish well-defined criteria for determining their identity.

of an outbreak in horses (Sulkin 1945) * Also, this virus has been recovered from bird mites by Reeves et al (1947), Hammon et al (1948), and by Sulkin and Izumi (1945) Laboratory transmission experiments with the view of demonstrating transovarian infection in mites are now in progress in this laboratory Evidence is also conclusive that reservoirs of the equine virus exist in wild and domestic animals including birds For a review of recent advances in the epidemiology of the arthropod borne virus encephalitides the reader is referred to the excellent article by Hammon (1948)

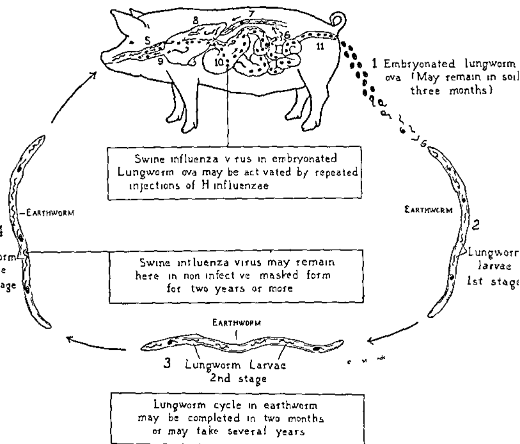


Fig 132—The swine lungworm as a reservoir and intermediate host for swine influenza virus (Shope)
Embryonated eggs which are laid by the adult female lungworm in the bronchi of the swine are coughed up swallowed and then eliminated in the feces 1 Upon ingestion by earthworms the lungworm eggs pass through developmental cycles 2 3 until the third larval ... e lungworm larvae is then eaten ... by way of the blood stream and ... mbryonated lungworm eggs which ... 9 swallowed 10 and eliminated ... 240 1944 by permission of the publisher)

*Since this manuscript was submitted for publication Howitt and her associates (1949) reported isolation of the virus of Eastern equine encephalomyelitis from chicken mites (*Dermanyssus gallinae*) and chicken lice (*Eomenacanthus stramineus*)

have been prepared by means of ultraviolet light irradiation and such antigens can be lyophilized and kept for long periods of time Only recently Casals (1945) described a simple method for producing avirulent mouse brain antigen for complement fixation tests by the application of heat at 60° C for thirty minutes The heated antigens retained a sufficiently high titer to warrant their use

Because of the increased interest in the development of complement fixing antigens derived from chick embryo and mouse brain tissues Cox (1948) and associates undertook development of antigens free from nonspecific factors They found that such antigens for a variety of neurotropic viruses could be prepared without appreciable loss in antigenicity by extraction in the desiccated state with benzene Such antigens are rapidly becoming available commercially In addition to its use with the virus encephalitides the complement fixation test has been found to be of practical value in the diagnosis of a number of other diseases of viral etiology including influenza lymphogranuloma venereum yellow fever and mumps The test appears to be of particular value in the diagnosis of those cases of acute aseptic meningoencephalitis in which previous involvement of the salivary glands was inapparent (Kane and Enders 1945)

Other developments in the field of virology have simplified procedures used in the diagnosis of this group of diseases For example the necessity for using bacteriologically sterile material in virus study has been largely overcome by the use of ether Zephiran the antibiotics and sulfonamide compounds to rid specimens of bacterial contaminants The use of bactericidal agents obviates the need for filtration which is frequently unsatisfactory because the viral agent may itself be retained along with the undesirable bacteria A number of reports have appeared in the literature concerning the usefulness of these bactericidal agents Ether may be used to destroy bacterial contaminants without affecting the poliomyelitis rabies or measles viruses Zephiran has been found satisfactory for the isolation of the influenza virus from throat washings With a few possible exceptions the growth of viruses in living hosts appears to be unaffected in the presence of a wide variety of antibiotics Reference has been made to the isolation of the herpes virus by primary inoculation of unfiltered sputums treated with penicillin (Rose et al 1945) The isolation of the mumps virus directly from human saliva by inoculation with penicillin into the amniotic cavity has also been reported (Beveridge Lind and Anderson 1946) Streptomycin and tyrothrycin were found useful in the isolation of psittacosis virus from fecal material by direct injection into the yolk sac of developing chick embryos (Morgan 1947a) The sulfonamides alone and in combination with antibiotics have proved useful in eliminating bacterial contaminants from specimens examined for various viruses

The discovery by Hirst (1941), and independently by McClelland and Hare (1941) that influenza virus possesses the capacity to agglutinate erythrocytes provided a valuable new approach to the study of viral agents The so called hemagglutination test is now widely used in the diagnosis of epidemic influenza and the antigenic pattern of strains of influenza isolated during different epidemics has been compared by means of this technic It is now

The procedures followed in the laboratory diagnosis of diseases caused by viruses are analogous to those used in bacterial infections. Conclusive evidence consists in the demonstration and identification of the virus. This may be accomplished in some of the virus diseases by using susceptible laboratory animals or chick embryos instead of the ordinary culture media used for the isolation of bacteria. Once the virus is recovered, identification is accomplished by determination of the animals for which it is pathogenic, routes by which it can be injected, tissues it infects, lesions produced, and through the use of the classical immunologic reactions, i.e., neutralization, complement fixation, agglutination, or precipitation reactions. The most conclusive evidence is available when virus has been recovered from a patient and an increase in neutralizing or complement fixing antibodies demonstrated in the convalescent serum of the same individual; nevertheless, laboratory studies have indicated that serologic procedures alone are valuable even in the absence of virus recovery. When it is not feasible to attempt recovery of virus from tissues, immunologic tests should be carried out using the blood serum obtained during the early stages of the disease and again after recovery of the patient. The presence of specific antibodies is of particular significance if blood specimens taken during the acute phase are negative and become positive with convalescence of the individual.

The clinical syndrome produced by some viruses is quite consistent, permitting the physician to make a proper diagnosis without resorting to laboratory aids. Typical of such diseases are measles, chickenpox, and smallpox. Again, some virus diseases cannot be differentiated until an etiologic diagnosis has been made and the causative agent has been identified by means of laboratory procedures. Thus, for example, the clinical, pathologic, and epidemiologic manifestations of the neurotropic virus diseases (excluding poliomyelitis and rabies) are so alike that it is practically impossible to establish the identity of a particular disease without the aid of laboratory studies. The "infectious encephalitides," embracing a number of distinct diseases of the central nervous system, must be identified etiologically if reliable epidemiologic data are to be obtained and if this group of diseases is to be properly classified. Knowledge concerning the "virus encephalitides" would be greatly enhanced if physicians made an earnest effort to secure laboratory aid for the identification of the causative virus.

Much work has been done in recent years to simplify laboratory procedures and attention has been directed toward the use of the complement fixation test for the diagnosis of the human virus encephalitides. The test described by Casals and Palacios (1941) and by Havens et al. (1943) is sufficiently specific to differentiate the various experimental infections caused by the neurotropic viruses. This test has already yielded encouraging results when used in the diagnosis of human infections induced by some of these viruses (Casals, 1947; Sulkin and Izumi, 1945). Because of the dangers inherent in the use of virulent antigens in these tests, attempts have been made to inactivate them without altering the efficacy of the material (Sulkin and Pike, 1949). Avirulent antigens

amount of protection is afforded by inactive viruses (equine encephalomyelitis, influenza, rabies and others). To be sure, immunity conferred with inactive agents is of short duration and vaccination should be repeated at frequent intervals.

In recent years efforts have been directed toward the development of prophylactic measures against various diseases through the use of attenuated and inactivated viruses. Epidemic influenza has received special attention. Various vaccines have been given parenterally while others have been given intranasally. The formalinized complex influenza A canine distemper vaccine of Horsfall and Lennette (1940) which received extensive clinical trial has been superseded by an influenza type A and B vaccine developed by wartime research. This vaccine which is now available for civilian use is effective in providing protection against the type A and B influenza viruses which have been the most prevalent causes of epidemics in recent years (Francis et al 1947). This vaccine contains influenza virus concentrated from allantoic fluid of developing chick embryos by adsorption on and elution from embryonic erythrocytes. During the winter of 1943-1944 extensive investigations of the prophylactic effect of influenza vaccination were carried out under the auspices of the Commission on Influenza of the Army Epidemiological Board. These studies indicate that subcutaneous vaccination of a human population with the newly described vaccine exerts a definite effect on the susceptibility to influenza A during an epidemic of high incidence (Francis 1945).

A number of investigators have emphasized that possible untoward reactions may be due to allergenic and anaphylactogenic properties of vaccines prepared from embryonic tissues of developing chicks. It has recently been suggested that intradermal injection of small doses of vaccine may obviate these difficulties. Van Gelder et al (1947) recently compared the rise in antihemagglutinins following intradermal and subcutaneous inoculation of concentrated vaccine prepared from strains of A and B influenza viruses. The intradermal dose which was about one tenth the subcutaneous dose induced a greater mean antibody response and the incidence of generalized reactions was lower in the group which received intradermal inoculations. Similar findings were recently reported by Weller et al (1948). Actually the prophylactic value of intradermal vaccination has not as yet been demonstrated.

Little attention has been given to the problem of passive immunity because of the transient nature of the protection conferred. Passive immunity can be produced experimentally, however, by intranasal instillation of small amounts of immune serum prior to inoculation with influenza virus. Russian investigators (Smorodintseff et al 1940) reported startling results following biweekly inhalations of vaporized antiserum given to a large number of individuals before and during an epidemic of influenza A. These observations were subsequently confirmed by Krueger et al (1944) who investigated the efficacy of this procedure in the prophylaxis and therapy of experimental influenza.

known that other agents including those of vaccinia variola fowlpox New castle disease ectromelia of mice mumps pneumonia virus of mice and pleuro pneumonia like organisms cause specific agglutination of erythrocytes With all of these agents the agglutination of erythrocytes may be inhibited by the addition of specific immune serum for this reason the reaction has already been widely applied to various aspects of virus research Recently two strains of mumps virus have been isolated directly from human penicillin treated saliva by inoculation into the amniotic cavity of the chick embryo and hemagglutinin was detected after three to four days incubation (Beveridge Lind and Anderson 1946) It has been suggested that the hemagglutination test with this virus may provide a more rapid and convenient diagnostic method for detecting increases in antibody concentration than other serologic procedures

Skin sensitivity tests are being developed which may prove valuable in the diagnosis of viral diseases A cutaneous sensitivity test is of particular value under circumstances where facilities for examining serum for specific antibodies are not readily available Such tests have been described for vaccinia and lymphogranuloma venereum but the latter is the only viral disease in which a skin test the Frei intradermal test is now widely employed as a diagnostic aid With improved methods for growing viruses in high titer there is reason to believe that intradermal reactions will be employed with increasing frequency In recent years a number of other intradermal tests with antigens of viral origin have been introduced Nagler (1944) and more recently Rose and Molloy (1947) reported specific dermal reactions in herpetic persons receiving intracutaneous injection of heat inactivated herpes virus cultivated in the chick embryo Since a positive reaction could be correlated with the presence of circulating antibody this test may eventually be of value in differential diagnosis Influenza virus produces a cutaneous reaction in most adults and in some children and it is possible according to Beveridge and Burnet (1944) that allergy to the virus may play a part in resistance to infection Whether or not this reaction will be useful in determining susceptibility to influenza remains to be seen A dermal sensitivity test for mumps using parotid glands of infected monkeys as antigen may be of value in the diagnosis of this disease It has been shown that persons exhibiting erythematous dermal reactions forty eight hours after inoculation of this material may be from the practical standpoint considered resistant to mumps (Enders et al 1946) Dermal sensitivity tests will undoubtedly be further investigated because of their potential importance as diagnostic procedures

Recommended laboratory procedures have been summarized by several investigators (Sulkin and Harford 1943 Sulkin 1943 Francis et al 1948 van Rooyen and Rhodes 1948)

PROPHYLAXIS

Earlier workers believed that artificial immunity could not be induced unless active virus was used in preparing the vaccines While this may be true in the case of some viruses it appears that in many cases a considerable

and highly antigenic but should contain several different strains of polio myelitis virus Extensive study in animals suggest promising results (Morgan et al , 1947)

Encouraging results with rabies and St Louis encephalitis viruses were also reported by Levinson et al (1945) with a vaccine similar to that just described (Milzer et al 1945) Several lots of rabies vaccine inactivated by this irradiation technic consistently induced a higher degree of immunity in mice than control phenolized vaccine The irradiated rabies vaccine showed no significant loss of potency after six months' storage at 5° C Similarly two lots of St Louis encephalitis vaccine inactivated by irradiation conferred a high degree of immunity in mice These reports are of a preliminary nature and the results cannot be evaluated until more extensive studies are available*

Sabin and Schlesinger (1945) reported the production of immunity to dengue fever with virus modified by propagation in mice These investigators observed that beginning with the seventh passage in mice the virus had undergone extensive modification in its pathogenic properties Human volunteers who were inoculated with the seventh ninth or tenth mouse passage dengue virus either alone or in combination with yellow fever vaccine were found to be immune when they were exposed to the bite of *Aedes aegypti* mosquitoes of proved infectivity Other volunteers who served as controls developed typically severe unmodified dengue

TREATMENT

A rational approach to research on the treatment of virus infections presents numerous difficulties because of the nature of the virus itself These agents multiply intracellularly and little is known regarding the mechanism of their pathogenesis Furthermore since viruses lack independent enzyme systems their metabolism must be intimately associated with that of the host cell Their only attribute of life appears to be their ability to reproduce and even here the energy of the host cell is necessary It is not therefore surprising that they have proved refractory to the antibiotic sulfonamide and other chemotherapeutic agents which have been so effective in combating other agents of disease On the basis of our present knowledge regarding these simpler forms of life the most promising method of attack with drugs would be that directed toward the reproductive process It is probable that the virus after gaining access to susceptible tissues of the host stimulates the cell in such a way that it is diverted from its normal function to that of synthesizing the virus complex Since these synthetic processes are presumed to be catalyzed by enzymes virus reproduction may be inhibited by the phenomenon of drug enzyme substrate competition

Sulfonamide therapy has proved successful in trachoma inclusion blennorrhea and lymphogranuloma venereum though there is increasing evidence that the causative agents of these diseases do not fall within the category

*Editor's note (O F) The Lederle Laboratories have recently developed an avian rabies vaccine which is very promising

For several years a living neurotropic strain of virus was used in vaccination against yellow fever Because of the pathogenicity of this virus for the nervous system vaccination of the human being was accompanied by adequate protecting doses of immune serum The development of a strain of virus attenuated by prolonged cultivation in vitro led to the production of a relatively safe vaccine which does not require the concomitant administration of immune serum The effectiveness of this vaccine which has been used extensively since 1937 has been indicated by the demonstration of protective antibodies in vaccinated persons and by the curtailment of epidemics of jungle yellow fever (Bugher and Gast Galvis 1944)

The need for an effective type of vaccination of man against the viruses of equine encephalomyelitis became apparent when reports appeared of the occurrence of human infection under natural conditions and laboratory infection resulting from exposure to the virus (Sulkin and Pike 1949) Beard et al (1940) vaccinated a group of laboratory workers with a formalin treated chick embryo vaccine prepared with Eastern and Western strains of equine encephalomyelitis No instance of infection by these agents has been observed in the vaccinated group These observations are significant in view of the high incidence of infection among laboratory workers with the Eastern or Western types or with the Venezuelan type of equine encephalomyelitis (Sulkin and Pike 1949) According to Beard et al (1941) the immunity induced in man by formalin treated vaccine is of a temporary nature requiring revaccination of those continually exposed to infection Immunity in horses resulting from actual infection is enduring in contrast to the immunity induced by injections of chemically treated vaccine (Cox and Olitsky 1936)

Not long ago Sabin (1943) undertook to develop suitable and safe vaccines for protection of human beings against the St Louis and Japanese B types of epidemic encephalitis The resulting vaccines in which the virus has been rendered noninfective by formalin were capable of conferring protection rapidly could retain their potency after storage for long periods of time and produced no ill effects on inoculation in healthy persons The effectiveness of these vaccines must await further trial under natural conditions (Sabin 1947 Warren Smadel and Rasmussen 1948)

Poliomyelitis has been intensively investigated in an effort to find a method of active immunization that will be both effective and safe Inactivated vaccines fail to produce satisfactory protection while vaccines containing active virus though possibly effective may lead to infection A few years ago two large scale experiments on active immunization of human beings were terminated because of this danger In 1945 Milzer et al using the mouse adapted Lansing strain of poliomyelitis virus described a completely inactivated vaccine which confers a high degree of protection against subsequent intracerebral inoculations in mice Since immunologically distinct strains of poliomyelitis virus are known to exist these workers suggest that a vaccine for prophylaxis against human poliomyelitis must not only be safe

In view of the apparent ineffectiveness of the various antibiotics, antisera and sulfonamides in the treatment of virus diseases another approach to the problem is indicated In the light of our knowledge today, treatment of virus diseases in general is largely a matter for future development

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of true viruses Scattered reports of successful treatment of other virus diseases have appeared but the observations still require confirmation Apparently, good results with certain therapeutic agents may be due either to mistaken diagnosis or to the beneficial effects of concomitant therapy These criticisms apply to certain studies indicating a favorable effect of the sulfonamides in the treatment of trachoma Favorable experimental results with sulfonamides in the treatment of lymphocytic choriomeningitis have not been consistent when effective they were dependent upon early administration and more nearly approached prophylaxis than treatment Sulfonamide therapy has been given extensive trial in patients with primary atypical pneumonia Neither symptomatic improvement nor alteration in the febrile course was observed with any degree of consistency many patients were even more uncomfortable when receiving the drugs Sufficient evidence exists to conclude that the sulfonamide drugs have no direct effect on infections caused by viruses Secondary infection of the vesicles in smallpox is believed to be responsible for much of the late toxemia in this disease It has been shown (Leishman 1944) that the administration of sulfonamides throughout the course of the infection has strikingly diminished the degree of secondary infection and consequently lessens mortality Penicillin has been observed to have a similar effect (Jeans Jeffrey and Gunders 1944)

Extensive attempts at serotherapy have likewise been unsuccessful in treatment of virus diseases The primary difficulty with serotherapy lies in the fact that viruses are intracellularly situated and the immune bodies cannot reach the infectious agent because they are unable to enter the cell Evidence also indicates that in most virus diseases all cells which are subject to infection have already been invaded by virus by the time symptoms appear Future success in the treatment of virus diseases with immune bodies will depend to a great extent upon the development of methods for earlier diagnosis For each intracellular parasite the appropriate time beyond which parenteral injection of antibodies is no longer effective must be determined experimentally Despite several reports to the contrary the treatment of virus diseases is of no value after the infection has become established Convalescent serum on the other hand has been employed with success in prophylaxis and in modifying the course of certain diseases including measles mumps and chicken pox The antibiotics have thus far been found to be almost wholly without beneficial effects in the treatment of virus diseases Heilman and Herrell (1944) found penicillin to be effective in the treatment of ornithosis but Kramer et al (1944) suggested that the action of penicillin was not curative even though the mice remained well for appreciable intervals of time since the virus could be recovered from the brain and other tissues of such animals Evidence is accumulating to indicate that aureomycin a new antibiotic prepared from *Streptomyces aureofaciens* and Chloromycetin may prove of value in the treatment of diseases caused by members of the psittacosis lymphogranuloma group

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Knowledge about this mode of transmission made it possible to combat yellow fever by controlling the vector. The first anti *aegypti* campaigns in Havana, Panama, and Rio de Janeiro gave spectacular results

The second fundamental discovery is the susceptibility of monkeys to yellow fever In 1927 Stokes, Bauer, and Hudson, working in Nigeria, West Africa, managed to produce yellow fever in the Asiatic *rhesus* monkey *(Macaca mulatta)*. Thus, it was possible to study the disease in a laboratory animal, and many uncertainties concerning its etiology, pathology, and immunology were elucidated, increasing enormously our knowledge about this illness

The third important discovery was made by Theiler in 1930 This worker demonstrated that yellow fever virus produced in white mice, when inoculated directly into the central nervous system, a fatal encephalitis with multiplication of the virus and permitting serial passage In this manner a laboratory animal became available which had many advantages over the *rhesus* monkey, because mice are more easily obtained and they are much cheaper Thus, studies of the virus progressed very rapidly, resulting, in a short while, in the development of an efficient vaccine and of a neutralization or protection test

The fourth discovery of great importance is the finding that yellow fever may exist in nature in the absence of *A aegypti*

In 1932, Soper studied an epidemic of yellow fever in the State of Espirito Santo, Brazil, in which the urban mosquito *A aegypti* could not be incriminated as the vector (Soper et al, 1933) Later, similar epidemics of great extension occurred in other regions of Brazil as well as in other South American countries this new epidemiologic modality of the disease has been called "jungle yellow fever"

GEOGRAPHIC DISTRIBUTION

Surveys dealing with the distribution of immunity have shown that yellow fever is much more widely distributed in Africa than was originally thought, and these studies have made it possible to determine the approximate boundaries of the immunity zone on that continent (Sawyer and Whitman, 1936) Studies made by Mahaffy, Smithburn, and Hughes (1946) indicate that the disease has recently occurred in the Belgian Congo, Uganda, Anglo Egyptian Sudan, Eritrea, Somaliland, Kenya Colony, and Northern Rhodesia To the east, positive tests have been obtained up to the coast of the Red Sea in Eritrea, and to the south all the way to Balovale in Northern Rhodesia In Tanganyika Territory and Zanzibar no indications of recent infection have been found Abyssinia has not been adequately studied

In Central America and Mexico the studies by Kumm and Crawford (1943), in which about 4,000 blood samples were collected in eighty five localities and examined for the presence of neutralizing antibodies, show that only in the region east of Panama have cases occurred in recent years Most of the South American countries have been visited by yellow fever since 1925, with the exception of Chile and Uruguay, in accordance with immunologic surveys (Soper, 1937)

It is the opinion of certain epidemiologists that the Amazon valley constitutes a permanent focus of yellow fever, which is principally maintained in jungle animals From this enormous endemic region epidemics originate from time to time and invade the more densely populated areas

The series of epidemics which broke out in the central and southern states of Brazil, beginning in 1934, are a classical example of this invasion (Soper, 1938) Starting in the state of Goiaz, the disease spread over the entire southern part of this state and a portion of the state of Minas (
during the succeeding
1935 to 1936, this time
ing during the winter and reappearing during the hot season, in contiguous regions, until the epidemic burned itself out after having passed through the southern part of the state of Minas Gerais as well as the states of Rio de Janeiro and Espirito Santo, and to the south through Paraná and Santa Catarina

CHAPTER 18

YELLOW FEVER

HENRIQUE DE AZEVEDO PENNA

Yellow fever is an acute infectious disease caused by a specific virus and transmitted by certain species of mosquitoes. It attacks man and certain sylvatic animals, especially monkeys, and occurs generally in the form of epidemics and epizootics. In nonfatal cases a permanent immunity is established.

HISTORY

Yellow fever probably has existed in America and Africa since time immemorial. However, the first descriptions which permit identification of this illness with some degree of certainty date from the middle of the seventeenth century in America,* and only in 1778 was it recognized in Africa† (Carter, 1931).

At the beginning a great variety of names was given to this disease. Among these may be mentioned *vomito prieto*, used by the early Spanish observers, which called attention to a very characteristic symptom. The name "yellow fever" was introduced later to describe this malady. It originates from the jaundice which so frequently is a part of the clinical picture (Griffith Hughes, 1750, cited by Carter).

During the eighteenth and nineteenth centuries this disease, which is essentially a tropical one, was carried to other regions by ships transporting not only people suffering from yellow fever but also the mosquito vector, which found suitable conditions for its propagation in the water containers on board.

Certain large cities became endemic foci and served as sources for disseminating the illness to regions far from the tropical zone. In these new regions it occurred in the form of epidemics which generally burned themselves out, as the vector could not survive the hardships of the cold season.

Various cities of the United States were thus stricken.

The epidemic in Cadiz, Spain, in 1730 marks the first introduction of this disease into Europe.

Whether yellow fever originated in Africa or America is a question which has been much discussed and probably a satisfactory answer will never be found. It is certain, however, that the virus must have been brought many times from Africa to America and carried there, especially on the slave ships.

The beginning of the twentieth century saw the start of an era which can appropriately be called the scientific era of yellow fever, during which various discoveries were made which constitute real milestones in the history of this disease.

The first of these discoveries is the transmission of the disease by the mosquito *Aedes (Stegomyia) aegypti*.‡ The study which proved this fact beyond a doubt was initiated in 1900 in Havana by the American Army Commission under the direction of Walter Reed (Senate Document No. 8[illegible], 1911). The theory that yellow fever was transmitted by *aegypti* had been formulated in 1881 by C. Finlay, chiefly on the basis of epidemiologic considerations.

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* The epidemic of Yucatan in 1648. Lopez de Cogolludo's report, 1688.

† Schotte's report published in [illegible]8[illegible], describing the epidemic in San Luis in Senegal, 1778.

‡ *Aedes (Stegomyia) aegypti* Linnaeus, 1762, is the correct name of the species. It should be noted, however, that this mosquito has been mentioned in the medical literature under many names, among others *Stegomyia fasciata* and *Aedes argenteus*.

icterohaemorrhagiae the cause of Weil's disease (Noguchi 1919, 1925) This point of view was widely accepted until 1927, when the possibility of studying the disease experimentally in monkeys furnished means of correcting this error

LABORATORY DIAGNOSIS

Isolation of Virus

To isolate virus blood or serum which has been taken from the patient during the first three days of fever is injected into a series of 6 or 12 white mice Each mouse is inoculated intracerebrally with 0 03 c c of the material which should preferably be injected immediately after it has been collected

If virus is present, the animals will become sick and die usually after a week It is advisable to make passages with the material from one of the sick mice to another group before trying to make an immunologic identification of the agent

Neutralization Test

The neutralization test serves a double purpose (1) to identify yellow fever virus and (2) to determine the presence of specific antibodies in a given serum sample

Identification of the Virus—After a few serial passages in the brains of white mice the virus adapts itself to and kills mice more regularly but after a longer interval than in the first passage A suspension in physiologic saline is prepared from the brains of mice which have become sick as a result of infection with this modified virus To various dilutions of this suspension a constant quantity of a known immune serum is added There should also be a control with a serum known to be nonimmune Each mixture is injected intracerebrally into a group of 6 or 12 mice The virus will be that of yellow fever if the immune serum protects the animals in one or more dilutions provided that mice which received normal serum and the virus succumb

Determination of the Presence of Specific Antibodies in a Serum.—The unknown serum is added to a filtered suspension of triturated brains from mice which have become sick after the inoculation of neurotropic yellow fever virus Generally desiccated material is used The dilution of the suspension is calculated in such a manner that a virus concentration is obtained which with certainty, can be neutralized by an equal volume of a standard immune serum, and which is sufficient to kill all the animals when mixed with the same volume of normal serum

Three hundredths of a cubic centimeter of the mixtures of unknown sera and the virus are injected cerebrally into each of 6 mice After a few days encephalitis can be noted in the animals if the sera do not contain neutralizing antibodies whereas all mice which received sera containing such antibodies will remain well These tests are usually made with many sera in a single run, always including controls with sera which are specifically known to be positive and negative (Theiler, 1933, Sawyer and Lloyd 1931)

This test serves to make an accurate diagnosis when made with two serum samples—one collected during the first days of the illness and the other during the convalescent period

In the case of yellow fever the first sample should be negative and the second positive

By means of protection or neutralization tests retrospective diagnoses of yellow fever can also be made in any given population and from the age of the youngest individual found immune the date of the last

By this means studies have been made to yellow fever which has been found to be anticipated (Sawyer, 1934)

For a decade, viscerotomy posts in the states of Amazonas and Para have consistently produced a few positive cases each year, indicating that the disease remains endemic in the forests of the Amazon river valley

No yellow fever exists in Asia The reason why the disease has not invaded certain points on the Asiatic continent, where the vector *A aegypti* is found in abundance, is not known

ETIOLOGIC AGENT

In 1901, the American Commission in Havana showed that the causative agent of yellow fever is filtrable through Berkefeld candles However, only after the discovery in 1927 of an animal in which the disease could be experimentally produced was it possible to demonstrate that this etiologic agent has the characteristics of a so called filtrable virus

In man the virus is found in the blood up to the third or fourth day of the disease Later it disappears from the circulation giving place to antibodies capable of neutralizing it During the period in which the virus is found in the blood of man and other susceptible vertebrates it may infect certain species of mosquitoes which feed thereon

The virus does not multiply in culture media which do not contain living cells

Yellow fever virus measures approximately 20 millimicrons (Findlay and Broom 1933 Pickels and Bauer 1940) and is therefore classified among the smallest of viruses It keeps poorly at room temperature At very low temperatures such as those obtained with dry ice (−78° C) it will remain active for long periods of time The best process of preservation however consists in desiccating the virus rapidly in a vacuum in the frozen state (Sawyer Lloyd and Kitchen 1929) When dry and kept in sealed glass containers it will *remain active for several months in a refrigerator (8° C) and for an almost indefinite period* of time at temperatures below 0° C

When inoculated into rhesus monkeys it will produce a disease similar to that found in man Other species of monkeys can also be infected but they rarely die the rhesus therefore has been particularly valuable for experimental work

When introduced into the central nervous system of white mice yellow fever virus produces a fatal encephalitis It can be kept alive through serial passages in this animal when inoculated by the intracerebral route After a certain number of passages alterations occur and as a result the virus will no longer produce yellow fever in man or monkeys This modified virus is called *neurotropic* and has been employed in the vaccination of human beings (Sawyer Kitchen and Lloyd 1932 Laigret 1934)

When inoculated into developing chick embryos a few days old the virus multiplies and can be maintained serially This observation has a practical application in the preparation of vaccine (Elmendorf and Smith 1937)

The virus also multiplies though such high titers are not obtained in embryonic tissues from mice or chickens maintained alive in vitro (Lloyd Theiler and Ricci 1936) Through serial cultures in embryonic tissue it has been possible to obtain a modification of the virus which has been extensively employed in the immunization of human beings This strain is known in the literature by its laboratory designation 17D (Theiler and Smith 1937a

The modification consists of an attenuation of the virulence resulting not only in *the disappearance of the property of producing yellow fever, but also in a greatly reduced* neurotropism or the capacity to produce encephalitis

Noguchi stated in 1919 that the etiologic agent of yellow fever was a filtrable Leptospira to which he gave the name *Leptospira icteroides* morphologically similar to *Leptospira*

placed in glass containers with a 10 per cent solution of *formalin in physiologic* saline, and afterward they are sent to the laboratory (Rickard, 1937)

Through the viscerotomy service, yellow fever has been discovered in various regions where its existence was not previously suspected (Soper, Rickard and Crawford, 1934) In Brazil alone there are 1,303 viscerotomy posts in operation, and during the past sixteen *years 365,584 liver specimens have been* collected and examined

Complement Fixation

Many attempts have been made to use the complement fixation reaction in yellow fever studies *Aragão, Moses, Frobisher, G E Davis, Lennette, and* Perlowagora are some of the investigators who have studied this problem

More recently Perlowagora and Hughes (1946), working with a purified antigen have obtained results useful for epidemiologic investigations

Since complement fixing antibodies in the blood of man and susceptible *animals disappear after a relatively short period of time, while neutralizing* antibodies persist, it is possible to draw conclusions regarding the probable date of infection by carrying out both tests simultaneously

EPIDEMIOLOGIC VARIETIES AND VECTORS

Immunologically, pathologically and clinically yellow *fever* is one and the same disease in America and in Africa Epidemiologically, however, two forms are recognized an *urban form* which is transmitted from man to man through the mosquito *A aegypti* and another variety known as *jungle yellow fever,* which is transmitted by vectors other than *A aegypti* (Soper 1936)

The presence of the virus, *of the aegypti* mosquito, and of a susceptible human population are the necessary factors for the maintenance of urban yellow fever

The virus is present in the blood stream of the patient up to the third day of the fever *A aegypti* which feed upon such blood become capable of transmitting the disease after a few days' period, which is called the *extrinsic incubation period* (Carter, 1900), and remain infective for the rest of their lives

The extrinsic incubation period, which in nature is about 12 days, can be interpreted as the time necessary for the virus to multiply in the mosquito so *that it reaches* the salivary glands

The life span of *A aegypti* is approximately three months.

Only the females feed on blood and are infected in nature

All experiments aimed at demonstrating hereditary transmission of the infection in mosquitoes have failed

A aegypti is essentially a domestic insect, which for oviposition *prefers small water* containers found inside of or in close proximity to human habitations

The immunity conferred by yellow fever is absolute and permanent, and therefore the urban form of the disease would disappear from a locality were it not *for the fact that* the susceptible population is renewed through the introduction of nonimmune individuals coming from other places, or infants born in that locality Such spontaneous elimination of the disease has in fact occurred, because in order *that this might happen it is not necessary* that

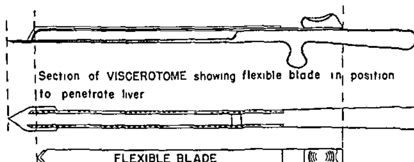
it is merely sufficient that the reduction of non

combating the vector has reduced the urban

form to a condition of secondary importance

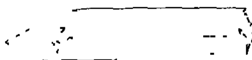
Viscerotomy

In fatal cases, histopathologic examination of the liver, when made by an expert, usually furnishes information of great diagnostic value Based on this fact, services for the collection of liver specimens on an extensive scale, from fatal cases of febrile illnesses of short duration, have been organized in various countries



Top view of viscerotome with flexible blade withdrawn

Drawing Nº 2


Cutting end of viscerotome with flexible blade in position to penetrate the abdominal wall of the body

Drawing Nº 3

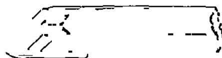

The same end of the viscerotome with the flexible blade in position to enter the liver

Fig 133

These liver specimens are removed from the cadaver by an instrument called viscerotome (Rickard, 1931), which has been distributed to special agents in the indicated zones "Viscerotomy" is easily done, and the collection of such material can be carried out by laymen The liver specimens are

and even vomiting Albuminuria is almost always present These sympt disappear within a few days and the patient recovers completely

The clinical diagnosis of this benign form of yellow fever can rarely made in isolated cases, that is to say, outside of epidemics It is, however, most common form of this disease and is responsible for the majority immune individuals found in nature

In more severe cases the general state of health declines rapidly symptoms of intoxication appear The patient is very restless Vomi occurs frequently and the vomitus may be of a dark color due to hemorrha in the gastric mucosa The stools may also be dark Jaundice appears patient shows great prostration Oliguria, followed by anuria and coma is p of the terminal picture when death occurs Fatalities most frequently oc between the fifth and the eighth day of illness

There exist however possibilities of survival even in very severe c showing all the symptoms of the so called classical cases

Some of the *symptoms* or phenomena deserve special mention

Frequently the *fever*, which is high at the onset (39° 40° C) does fall much during the course of the disease, whereas the rapid pulse no initially slows down causing a discrepancy between the pulse and the te perature, which is known in the literature as *Faget's sign* (Faget 1875)

Albuminuria is one of the most common symptoms and is of considera value for clinical diagnosis In benign cases it may be very slight but it rarely absent In severe cases it is very intense and may be measured in gra per liter Almost always albuminuria is present from the onset

Pronounced *oliguria* is a symptom of the advanced phase of the disease a is an important factor in giving a bad prognosis

Hemorrhages during the initial phase are almost invariably related to t nasal mucosa and the gums If this blood enters the stomach it may la be vomited in the form of black vomit However, the real black vomit is deriv from hemorrhages in the gastric mucosa and is rarely encountered in the init stages In some cases where violent hemorrhages are involved unaltered blo is vomited because sufficient time has not elapsed to permit the action of t gastric juices At times hemorrhages may be generalized hematemesis meler epistaxis and cutaneous hemorrhages occurring simultaneously

The *jaundice* in yellow fever is in many cases not as striking as the nar of the disease might indicate and it appears relatively late Frequently it only a yellowish tinge most noticeable in the sclerae becoming more pronounce toward the end of the disease There are, however, cases in which the jaundi is intense After death it is generally more easily recognized

The clinical diagnosis during epidemics can usually be made with co siderable certainty in the more severe cases and with reasonable accurac in benign ones The diagnosis of isolated cases however, should always b based on laboratory procedures among which the most exact is *the isolatio* and identification of the virus If this is not possible, then one may compar

The *jungle form* was recognized for the first time in 1932 during an epidemic in Vale do Canaa, Espirito Santo, Brazil (Soper et al 1933). It was not possible at that time to determine the vector.

Following this outbreak various epidemics were observed in Brazil as well as in other South American countries, which furnished opportunities for the study of the epidemiologic characteristics of this form of the disease.

Only persons who live near the woods or who enter the forest by chance or to work are attacked.

It seems to be well established that the virus can exist and propagate in the forest without the presence of human beings and that the latter frequently play the role of accidental victims only.

Neutralizing antibodies against the virus have been found in the blood of forest animals, especially monkeys, which indicates that some of them are infected in nature. On one occasion yellow fever virus was isolated from the blood of marmosets captured in the woods near Ilhéus in the state of Bahia, Brazil, without the appearance of any known human cases in that neighborhood (Laemmert, Ferreira and Taylor 1946).

Yellow fever virus was isolated from *Haemagogus capricornii* Lutz and *Aedes leucocelaenus* Dyar and Shannon (Shannon et al 1938).

Bugher et al (1944) showed that Haemagogus mosquitoes were more abundant in the tree tops, which seemed to be their natural habitat. Mosquito captures which until then had been made at ground level did not furnish a true indication of the abundance of these insects in the forest. This observation explained the apparent scarcity of Haemagogus mosquitoes in woods where the disease was known to exist, the survival of the virus from one rainy season to another, as well as the occurrence of a great number of cases of yellow fever among wood cutters.

In Africa it has been difficult to prove the existence of jungle yellow fever, that is to say, the transmission of the disease by mosquitoes other than *A. aegypti*, principally due to the wide dissemination of that species. In various regions of Africa this insect shows an unusual type of behavior, being found in uninhabited forests where it breeds in tree holes.

During an epidemic in 1941 in the proximity of the Semliki forest, Uganda, yellow fever virus was isolated from two lots of *A. (Stegomyia) simpsoni*. The immunity rate in monkeys captured in that area was 61 per cent.

In 1942 the virus was again isolated from *A. simpsoni* in the complete absence of any known human cases, which indicated the probable existence of an extrahuman cycle.

As *A. simpsoni* normally inhabits the forest edges, further searches for other sylvatic vectors were made and in April 1944 virus was isolated from a group of Aedes captured in the interior of the Semliki forest, which included neither *A. aegypti* nor *A. simpsoni*. This observation demonstrated the existence of yellow fever in Africa in the absence of human beings, as the Semliki forest is not inhabited by man (Smithburn and Haddow 1946). *A. africanus* appears to be the forest species most likely to be implicated.

CLINICAL FORMS, SYMPTOMS, DIAGNOSIS AND TREATMENT

There is a great variation in the severity of yellow fever. Generally two distinct phases mark the course of the disease: the first, a period of general reaction or infection, and the second, a period of intoxication in which the symptoms are principally caused by liver damage. In many cases the symptoms are so mild and noncharacteristic that yellow fever is not diagnosed at all but receives a vague denomination such as grippe.

On opening the abdominal cavity, a brownish yellow color of the liv is noted which becomes even more evident after the organ has been remove and exsanguinated This color is said to resemble chamois yellow or the colo of boxwood

The lobular pattern is distinguishable on cut section which shows the sam coloration as the surface of the liver There is no alteration in the size of th organ

The dark contents of the stomach can generally be seen through its wal After opening the contents are found to consist of dark brown material whic has often been compared to coffee grounds On other occasions the stomac contains a yellowish fluid in which dark particles of partially digested bloo are floating In the gastric mucosa there will be found aside from capillar congestion varying numbers of small black spots corresponding to the place where hemorrhages have occurred

Macroscopic examination of the other organs will reveal nothing unusual except the general yellowish tinge which is most marked in such places as the subcutaneous tissues or the inner surface of the large blood vessels and in dications of hemorrhages which may be found in almost any organ

The macroscopic lesions encountered at autopsy are not of a nature which permit an undoubted diagnosis of yellow fever and indeed several other dis eases may present a similar appearance especially certain types of poison ing

Microscopic examination reveals lesions of the kidneys heart spleen and other organs

It is in the liver however that pathologic changes of the greatest diagnostic value are to be found Examining the tissue with the low power of the micro scope a certain disorganization of the parenchyma can be distinguished which is most apparent in the midzone of the lobule There is a jumbling of the liver cords with distortion of the sinusoids The presence of fatty droplets in the cytoplasm of the hepatic cells is a constant finding

The principal lesion however, is the necrosis of the parenchymatous cells In sections stained with hematoxylin and eosin the necrotic cells stand out as rounded bodies highly acidophilic and surrounded by a narrow clear zone as if shrunk Nuclei also acidophilic may be distinguished from the cytoplasm only with difficulty In such cells a nucleus is sometimes found flattened against its surface and believed to belong to a phagocytic cell Councilman (1890) was the first to describe the appearance of the necrotic liver cell in yellow fever and for that reason cells or parts of cells with this type of de generation are known as Councilman bodies" The distribution of these bodies in the microscopic section is very characteristic They are scattered over almost the entire lobule in an irregular manner usually isolated and are more abundant in the midzone of the lobule Rocha Lima (1912) called attention to this midlobular predominance and to the spotty distribution of the necrotic cells There is no tendency to focal necrosis and all lobules are

two blood samples for the presence of specific antibodies The first sample should be taken during the first three days of illness and the second during the period of convalescence

In fatal cases histopathologic examination of the liver usually permits the making of a definite diagnosis

Among those diseases which occur in epidemic form and which may show a resemblance to yellow fever one might mention Weil's disease malaria relapsing fever and dengue In the first three the identification of the etiologic agent establishes the diagnosis The absence of severe or fatal cases in dengue is an important characteristic in differentiating the two diseases

No specific treatment is known against yellow fever

The application of immune serum is of value only as a prophylactic measure

When the serum is introduced before or simultaneously with the virus in experimental inoculation it prevents the disease The intracellular habitat of the virus does not permit antibodies introduced after the virus to exert any effect at all

Liver necrosis which is the principal lesion responsible for the symptoms of the disease develops rapidly and since it is an irreversible process it is not susceptible to any treatment whatsoever

Experiments directed at neutralizing the toxic effect caused by the destruction of the liver the administration of calcium salts which has given satisfactory results in certain other intoxications also caused by liver necrosis have been in vain *

It is however advisable to follow certain general rules in the symptomatic treatment of patients (Soper 1942)

Transportation of the patient from one locality to another should be avoided

A laxative may be given on the first day The food intake should be limited to fruit juices

Depressant antipyretics should not be used

Convalescence is at times prolonged The patient should therefore not reassume his activities too soon particularly if they involve heavy physical exertion

MORBID ANATOMY

The general appearance of the cadaver in yellow fever is not characteristic

Jaundice when present is more easily recognized than during life In certain regions ecchymotic patches on the icteric skin produce a purplish appearance

Flecks of dried blood around the mouth and nostrils indicate the occurrence of hemorrhages

*One of the editors (O F) recently suggested the use of vitamin B_1 and methione

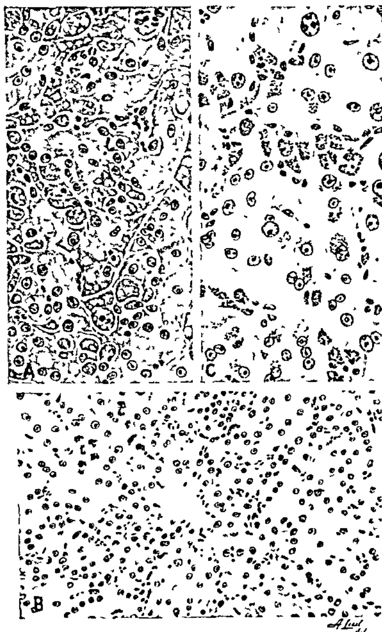


PLATE II — *A* Classical picture of yellow fever in section of human liver stained with hematoxylin and eosin. Councilman bodies are distributed throughout.

B and *C* Sections of human liver in which the classical picture is not found but in which bright ochre-colored granular bodies are scattered throughout the lobule with the greatest concentration in the midzone. These granular bodies have been used as a basis for the diagnosis of yellow fever in cases in which eosinophilic Councilman bodies could not be found.

(From Villela, F.: Histology of Human Yellow Fever when Death Is Delayed. Arch. Path. **31**: 665-669, 1941. Reproduced by permission Archives of Pathology, the American Medical Association and the Rockefeller Foundation.)

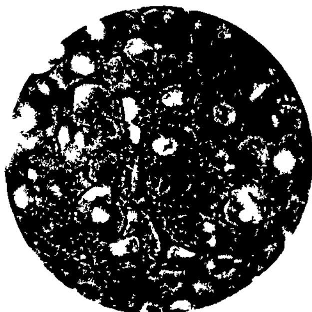


PLATE III —H tolo e t on of ell fe r l er sta ed tl l en atox l n a l eos n O l mne s on ol je t e An co o or f ln

Coun ilman l od es sta ne l p nk A nu l u bel e ed to elo to a pl ocyt c cell can be seen fl ttened aga nst one of tl e e l od e

curred between the eighth and seventeenth day The diagnosis was based on the presence of rounded granular bodies of a vivid ochre yellow color predominantly distributed in the midzone of the lobule Villela believed that they represent Councilman bodies already in a stage of disintegration

When viscerotomy service was begun in Brazil it was believed that the microscopic findings in the liver were sufficiently characteristic to permit the establishment of a diagnosis per se As wider experience was gained from suspect cases and through field investigations it was found that other diseases might show similar findings or even reproduce the histologic picture of the yellow fever liver

Only an examiner with great practice is therefore in a position to distinguish the lesions found in yellow fever from those encountered in certain rare cases of acute yellow atrophy, peritonitis meningitis poisoning with arsenic antimony or carbon tetrachloride the latter being widely used as a vermifuge

Belt (1939) described liver lesions found in cases of severe burns which had been treated with tannic acid and these lesions were indistinguishable from those produced by yellow fever

However none of these observations are of such a nature as to interfere seriously with the practical value of viscerotomy

In the majority of cases an expert can make the distinction and field investigations usually clear up the remainder of cases in which confusion still persists

PROPHYLAXIS

Anti Aegypti Measures

The maintenance of urban yellow fever depends on the cycle man-*aegypti* man

The most practical method of interrupting this cycle and thus controlling the disease consists in combating the mosquito

In order for yellow fever to disappear from a locality it is not necessary to eliminate the vector completely It is sufficient to reduce it below a critical number (Carter 1931)

The *aegypti index* is the per cent of houses found harboring larval foci

In the past it was believed that only the big urban centers could maintain the disease endemically due to the constant introduction of nonimmune individuals and that if these seedbeds were destroyed the disease would disappear from all nearby places through the process of spontaneous elimination

Although this program of mosquito control in key centers proved successful in certain places it failed in others

In the northeastern part of Brazil for instance during the campaign which began in 1923 with the cooperation of the Rockefeller Foundation yellow fever disappeared from the principal cities on the coast but continued to occur in villages and among the smaller towns of the interior

The demonstration of the existence of the jungle form of the disease and of the possibility of the importation of the virus from the forests to the cities

uniformly affected. Even in cases where the major part of the liver cells are necrotic some cells can still be seen around the central vein which have not been affected.

The degree of necrosis varies from individual to individual, ranging from 5 to 100 per cent, with an average of 80 per cent in a series of cases studied by Klotz and Belt (1930a).

The cells which have not undergone necrosis present different stages of degeneration from cloudy swelling to an advanced stage of necrobiosis. Such necrobiotic cells are characterized chiefly by a granular and vacuolated appearance of the cytoplasm and are generally increased in size. The nuclei show swelling and margination of the chromatin and one or more nucleoli are easily visible. Sometimes acidophilic substances are encountered in the nuclei forming aggregations which Torres (1928, 1931) identified as nuclear

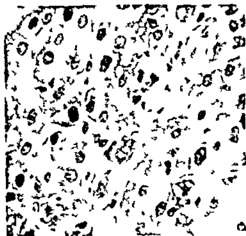


Fig 134—Biopsy of the liver in yellow fever showing fatty degeneration and acidophilic cells (Courtesy of Oscar Felsenfeld)

inclusions. In human viscerotomy material collected in Brazil nuclear inclusion bodies are rarely found and can be considered as exceptional so that they are of diagnostic value only when present. In the experimental disease in rhesus monkeys, on the other hand, intranuclear inclusions almost invariably form part of the histologic picture and are thus of value in making the diagnosis. They may also be found in the nuclei of certain cells of the nervous system in mice and monkeys which have died from yellow fever virus encephalitis.

The alterations found in the liver are of a degenerative character rather than inflammatory, although some leucocytes may be encountered.

In cases that survive, regeneration of the liver tissues is rapid and complete, with no residual fibrosis (Klotz and Belt 1930b).

Villela (1941) described a histopathologic picture in the liver which permits the diagnosis when death is delayed and presumably is caused by some intercurrent disease. Twenty three cases were studied where death had oc

tinued to be injected simultaneously (Lloyd Theiler, and Ricci, 1936) In order to reduce the volume of the serum injected, hyperimmune monkey serum was later employed This was obtained by injecting massive doses of the virus into an already immune rhesus monkey and collecting the serum nine days later when the maximum concentration of antibodies occurs (Theiler and Smith 1936)

Beginning with 1937 however a strain of virus so attenuated that it no longer requires the complementary use of immune serum has been employed on a large scale for the immunization of human beings

This modification of the virus was obtained by serial cultures in chick embryo tissues from which the major portion of the nervous tissue had been removed This strain is known as 17D (Theiler and Smith 1937a 1937b)

Several million people have already been vaccinated with the 17D strain of yellow fever virus principally in Brazil and among the Armed Forces of the United States

At the time when the vaccine is to be used it is diluted to contain not less than 1 000 MLD for mice to each 0 5 c c the volume injected into each person preferably subcutaneously *

Certain accidents have occurred during mass vaccination campaigns of which the most serious was the appearance of jaundice among persons vaccinated This illness is known as homologous serum jaundice

Postvaccination cases of jaundice of late appearance had already been reported by Findlay and MacCallum (1937) in England and by Soper and Smith (1938) in Brazil after vaccination with modified virus and supplementary immune serum

When the 17D strain of virus was first used without immune serum more than a million persons were vaccinated without cases of jaundice having been known to occur

At the beginning of 1940 an outbreak of postvaccination jaundice was observed in the state of Espirito Santo Brazil where more than a thousand cases were investigated which were principally related to the use of two vaccine lots believed to have been contaminated by an icterogenic agent derived from what was supposed to be normal human serum that had been used in the preparation of those lots of vaccine Some fatal cases were recorded The principal lesions were found in the liver and corresponded essentially to those described in cases of acute or subacute yellow atrophy of the liver (Fox et al 1942)

In 1942 another outbreak of postvaccination jaundice was noted among the Armed Forces of the United States (Sawyer et al 1944)

These accidents caused a temporary interruption of the vaccination program and investigators directed their efforts to finding means of perfecting the methods of preparing vaccine so as to eliminate the possibility of contamination by such icterogenic agents

*Editor's note (O F) Fox et al (Am J Hyg 38 113 1943) recommended only 500 MLD (LD_{50}) for mice for human vaccination

where it may be spread by *A aegypti* finally brought an end to this key center theory and indicated the necessity of a program of eradication wherever *A aegypti* were found (Soper and Wilson 1942)

The anti *aegypti* measures adopted by the National Yellow Fever Service of Brazil may serve as a model for similar campaigns that may be organized in other countries because the efficiency of the methods finally adopted has been tested through many years of practical application

Brazil which extends over a territory that measures 8 542 000 square kilometers has been divided for administrative purposes into six "circumscriptions" and these in turn in sixteen sectors each directed by a specialist

Some of the procedures used in the beginning such as quarantine isolation of the patient and destruction of adult mosquitoes by fumigation were abandoned in favor of antilarval measures directed against the foci of *A aegypti*

The search for and destruction of these foci are handled by a large group of sanitary inspectors who examine buildings and deal with potential mosquito breeding places by oiling

Other specialized groups of inspectors are employed in the capture of adult mosquitoes in order to give a better orientation to those who are searching for hidden breeding places that may have escaped attention on previous inspections

Successive areas are worked in territorial sequence and those already clean are carefully watched

The final objective is the complete eradication of *A aegypti* from vast areas rather than merely reducing the numbers below the critical level (Soper Wilson Lima and Antunes 1943)

Vaccination

The first attempts at vaccination were made with virus which had been inactivated by chemical substances Results were unsatisfactory

In 1931 in an attempt to put an end to the long series of laboratory infections that were occurring in New York and Africa a certain number of individuals were experimentally vaccinated with active virus The strain used was the one adapted to the nervous system of mice or the so called neurotropic virus This virus when injected subcutaneously into rhesus monkeys confers immunity without producing yellow fever On the other hand when it is injected intracerebrally it produces fatal encephalitis However even when injected subcutaneously it did produce encephalitis in certain exceptional cases For that reason it was considered dangerous to use this strain for vaccination of human beings without simultaneously injecting an adequate amount of immune serum The immunity conferred by the application of this method was satisfactory and no further accidental laboratory infections were recorded (Sawyer Kitchen and Lloyd 1932)

In 1935 the neurotropic virus was substituted for an attenuated virus by cultures in embryonic mouse tissue (strain 17E), but the immune serum con

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Yellow fever virus does not pass bacteriologic filters well unless its vehicle contains a high percentage of proteins Human serum was added to the vaccine in order to facilitate this filtration process primarily because it was believed to be harmless when inoculated into man The icterogenic agent *which is filtrable and resists heating at 56° C for half an hour was intro*duced inadvertently into the vaccine with this serum component

In order to prevent this hazard filtration of the vaccine has been discontinued and bacteriologic sterility now depends exclusively on rigorous aseptic precautions

No more cases of jaundice have occurred since the adoption of this modification in the technic employed in the preparation of vaccine

Encephalitis vaccination methods utilizing the Dakar strain from mouse brain suspended in arabic gum have been adopted by the Pasteur Institute in French West Africa and have been employed on a large scale in the French colonies in that area Laigret (1934) used three subcutaneous injections in progressively decreasing dilutions spaced over a few days This method although it confers a good immunity caused the occasional appearance of unpleasant reactions which at times involved the nervous system (Sorel 1936)

Since 1939 the French method has consisted of cutaneous scarifications sometimes together with smallpox vaccine

The scratch method simplifies the technic of application 7 890 417 vaccinations having been given in French West Africa from 1939 to 1943 without any serious reactions having been recorded (Rapport sur le fonctionnement technique de l'Institut Pasteur de l Afrique Occidental Française en 1943)

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CHAPTER 19

DENGUE AND DENGUE-LIKE FEVERS

Gustavo Pittaluga

DENGUE

Dengue is a benign disease that may assume such widespread epidemic proportions as to become a serious community problem

HISTORY AND GEOGRAPHIC DISTRIBUTION

The term "dengue" was first used in Mexico during the epidemic of 1824 to 1828 This epidemic covered the Atlantic side of the intertropical zone of North America, from South Carolina (U S A) to the Antilles and Venezuela, and particularly the Mexican coast The name is derived from the Spanish word *derrengado* (bent, crooked) or *abatido* (dejected), or from the Spanish American *denguero* (prudish, affected) or *amanerado* (full of mannerisms), and refers to the state of asthenia so characteristically observed in these patients In 1869, the Royal College of Physicians of London adopted this name in its nomenclature, giving the term "dengue" preference over other names for the disease in Europe and America—"*colorado*" (smutty or ruddy), "pantomime," "influenza," "dandy fever," "break bone fever," etc

This disease was first identified as a specific clinical entity in North and South America and the Antilles by the Spanish and French in the middle of the seventeenth century At first (Boyce, 1910) it was called *chapetonada* (a disease of Europeans due to change of climate) because of the eruption It was considered an "acclimatization fever" Others in Guadalupe (1648) described an epidemic of a disease with similar symptoms, and called it *coup de barre* (Finlay, 1912, Levaditi and Lepine, 1938) Later, especially during the nineteenth century, dengu[illegible] on the southern coast of [illegible] in Greece (1845 1865), [illegible] ports (1889), and again in America, from Louisiana (30,000 cases in 1922) down the coast of Mexico as far south as Venezuela, and down to Rio de Janeiro Last, a serious pandemic occurred in Greece and the eastern Mediterranean area in 1927 1928, with an extensive outbreak in Spain This ended, for a time, the epidemic cycles of dengue, with endemic foci left in many places I personally observed the epidemics in Greece and Spain (1928) and later studied a more limited outbreak in Havana (Cuba) in October November, 1944 (Pittaluga, 1945)

SYMPTOMATOLOGY AND DEVELOPMENT OF THE CLINICAL SYNDROME

The disease usually lasts 5 or 6 days The period of incubation is brief 2 to 7 days (*Zuelzer, 1874, Guiteras and Cartaya*, 1906, Manoussakis, 1928; Simmons, 1931) The prodromal period is mild Healthy individuals experience a *mild headache, general indefinite malaise*, and at times a state of excitation at the beginning of the disease The following day there is rapid *elevation of temperature*, 38 5° *to* 39° C, in some cases as high as 40° C, and

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erythema of rubeola It varies in color and intensity, according to the endocrine and neurovegetative condition of the patients The rash lasts approximately 2 or 3 days On the sixth or seventh day there is a light epidermic desquamation scarcely appreciable in most cases In some cases, a singular symptom is observed consisting of acroerythroderma, with slight edema of the palms of the hands paresthesia, cramps and itching In some cases there is pronounced muscular asthenia accompanied by diffuse pain in the muscles drawing sensation and in rare cases signs of slight cardiac dysfunction Acroerythroderma when present, often lasts 3 or 4 days The neuromuscular asthenia lasts a week or longer after all other symptoms have disappeared Generally on the seventh day the symptoms subside No splenomegaly is noted There is however a mild hepatic congestion No catarrhal or mucous inflammation of the respiratory tract is observed, nor pulmonary symptoms except in patients with previous bronchopulmonary affections of other origin which may be exacerbated In rare cases a slight subicteric tinge is observed Pronounced photophobia, persistent insomnia vomiting and small mucous hemorrhages (mouth intestine) may be present in some cases but do not constitute true elements of the syndrome More frequently there is slight albuminuria with barely observable traces of albumin, without renal lesions The pulse rate does not increase with the rise in temperature. There is a bradycardia with rarely more than 90 to 100 beats per minute even during the height of the fever The blood pressure is often low Convalescence may be prolonged for 2 or 3 weeks The mortality of this disease, if uncomplicated is nil With the exception of rare complications that originate in some previous illness all patients recover

HEMATOLOGY AND SEROLOGY

Dengue does not cause anemia The red blood cell count usually remains within normal limits, falling at the most, to 4 500 000 on the fifth or sixth day Loss of red blood cells is therefore, very slight, but there may be mild hematoxic signs such as anisocytosis and poikilocytosis Leucopenia is a constant finding In my experience the count fluctuates between 1 000 and 4 000 leucocytes per cubic millimeter on the fifth day, although in most cases it is not below 3 000 (Stitt, 1907, Joannides 1930, Simmons, St John and Reynolds 1931 Pittaluga 1945) The leucopenia is accompanied by a relative monocytosis which may be as high as 14 per cent according to Joannides and others (1930) There may be toxic changes, both cytoplasmic and nuclear, of the neutrophilic granulocytes often with karyorrhexis (fragmentation of the nuclear mass) and pathologic granules There is a left shift in the differential picture Young forms, metamyelocytes and stabs, increase beginning on the third day The differential count and the white count return to normal soon after the beginning of convalescence No immature or pathologic cells have ever been observed in the blood stream (Simmons et al, 1931, Pittaluga 1945)

Coles (1937) described the presence of small endoglobular corpuscles in blood preparations from dengue patients This finding has not been confirmed by other observers

an intense headache severe enough to confine the patient to bed The he ache seldom has the characteristics of migraine It is a cranial pain, so times so pronounced that it requires not only the usual sedatives to wh it responds very little but also the application of ice bags Soon also anorexia occurs at times with veritable pronounced food repugnance th and constipation are also symptoms

These symptoms are accompanied by spasmodic epigastric sensation w out true pain without rigid or painful abdomen without any diarrhea but polyuria and pollakiuria lasting 2 to 3 days It shows at times from

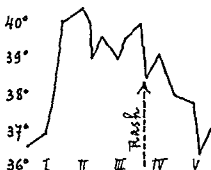


Fig 135 —Temperature curve and appearance of the rash (between the third and fo day) in a case of dengue observed in Greece (Manousakis

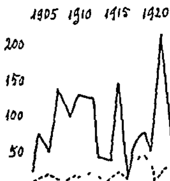


Fig 136 —Graph showing the number of cases of dengue in American soldiers (——— as compared with native patients) in the Philippines from 1905 to 1920 (fig show the percentages for 1 000 individuals in each group) (Silver Hall Hitchens)

first day on a cutaneous hyperemia principally on the face and upper part the body which has an aspect of transitory diffuse hyperemia On the third fourth day there occurs a true exanthem In connection with the sympto described above there appears a crisis the intense headache disappears the fever which tends to be low from the third day becomes normal or some patients there is fleeting hypothermia with more or less marked asthe which can induce a state of syncope The tongue in this period is thic coated There is an eruptive polymorphous rash appearing much like

intensity of propagation, the virulence of the epidemic is shortly exhausted and remains for years in a latent state, with rare sporadic cases among persons not immunized by previous epidemics (Blanc 1938, van Rooyen and Rhodes, 1940)

PATHOGENIC AGENT

It is not necessary to consider here the hypotheses or supposed discoveries of pathogenic agents of dengue which have never been confirmed McMullin (1919) suggested the possibility that dengue is simply an allergic manifestation caused by repeated inoculations of *proteins contained in the fluid* from the salivary glands of mosquitoes We must recall the mistaken theory of the spirochetal nature of the virus of yellow fever which followed *Noguchi's error* (1919) with respect to *Leptospira icteroides* Finally, the possibility of Rickettsiae (Sellards and Siler, 1928) in mosquitoes of the Aëdes genus infected by dengue patients was also disproved and abandoned

The work of Ashburn and Craig in the Philippines (1907) initiated the scientific studies of dengue virus The combined results of the investigations carried out in the last few years are as follows (Blanc, 1938, van Rooyen and Rhodes, 1940) The virus passes through most filters and is found in high concentration in the blood during the period of fever (Blanc and Caminopetros; Manoussakis, 1928, Kligler and Aschner, 1928; Simmons et al, 1931) Cultures in the chick embryo, obtained by Shortt, Rao, and Swaminath (1936), with blood from cases of dengue have caused lesions on the chorio allantoic *membrane*

The virus retains its virulence in the serum of patients at room temperature *for one to two months, according to Blanc and Caminopetros* (1930) The virus resists temperatures as low as -20° C for at least 48 hours (Holt, Fleming, and Kintner, 1931), *and* x-rays and ultraviolet rays Hoffmann, Mertens and Snijder (1932), in Amsterdam, succeeded in transmitting the disease to volunteers by injection of desiccated blood serum shipped from Java and preserved for 285 days Manoussakis demonstrated that the virus is destroyed by heat of 50° C for one half hour

Direct transmission of infected blood to normal individuals causes a typical disease—experimental dengue Mosquitoes become infected when they feed on patients during the first three days of the disease After the fourth *day, the proportion of infected* mosquitoes seems to be less (Kamal) Chandler, Blanc, Caminopetros, and others succeeded in infecting groups of Aëdes mosquitoes with blood of patients on the fifth day of infection The virus can be found in the cerebrospinal fluid *Nasopharyngeal* exudate and urine have always been negative as infecting agents

TRANSMITTING INSECTS

In the Mediterranean basin and in Africa and Central American foci, *A aegypti* is the transmitter In the Philippines, Simmons et al (1930) demonstrated that two species of the same genus, *A albopictus* and *A scutellaris*, can be vectors *A albopictus* is also found in Sumatra, according to Snijder, *Dinger*, and *Schuffner* (1931), who succeeded in [illegible] reproducing typical

Degenerative changes in the leucocytes, particularly the polymorphonuclears, have been ascribed to a circulating leucotoxin in the plasma, perhaps with myelotoxic action (Joannides) This may account for the leucopenia Experimental proof is lacking

Serologic investigations are negative* The serum of patients after an attack of dengue does not seem to contain antibodies capable of neutralizing the virus Blanc and Caminopetros proved during the Greek epidemic that the plasma or the serum of convalescent patients has no protective action in vivo or in vitro (Blanc and Caminopetros in Levaditi 1938)

PATHOLOGIC ANATOMY AND PATHOLOGY

Autopsies have rarely been performed in dengue The pathologic findings reported by some investigators (Corpanaris 1928 Photakis 1929), during the great epidemic, must be accepted with reservations because of the possibility of other existing pathologic processes The only lesions attributable to dengue are hepatic congestion with slight hepatitis without inflammatory foci slight myocarditis congestion or hemorrhagic lesions of the gastrointestinal mucosa Spleen and adrenals are normal There are no lymphatic glandular inflammatory reactions

EPIDEMIOLOGY AND TRANSMISSION

Epidemics of dengue correspond to the geographic distribution of mosquitoes of the genus Aedes (Stegomyia) Graham in Syria (Beyrouth, 1903) first demonstrated the transfer of dengue by mosquitoes without giving the exact species of the vector Later, Cleland, Bradley, and McDonald (1916) in Australia and Siler, Hall, and Hitchens (1926) in the Philippines excluded mosquitoes of the genus Culex, particularly *Culex fatigans* although transmission of the disease in the eastern part of the Mediterranean had been attributed to this species Siler, Hall and Hitchens (1926) proved that transmission is effected by mosquitoes of the genus Aedes particularly by *A aegypti (Stegomyia fasciata)* The great epidemic in Greece in 1928 verified these facts in an incontroversial way Blanc and collaborators (1938) showed that there were two successive epidemics one in the fall of 1927 with approximately 20,000 cases, another from June through October, 1928 The following year 1929, cases appeared only sporadically The number of known cases between July and October of 1928 in the Greek provinces in which Aedes mosquitoes are abundant was close to 800 000 in the districts of Western Macedonia where Aedes is rarely found if found at all, a total of 16[illegible] cases was reported The epidemic of "colorado"† ("ruddy fever") in Andalusia (Spain) in the same year in the Mediterranean littoral and along the river valleys was not seen in areas where the Aedes mosquito is found In the Philippines Simmons et al (1930) confirmed the epidemiologic and experimental data by demonstrating that a local species of the mosquito, *Aedes albopictus* transmits the dengue virus It is apparent, then that the old hypothesis previously presented in Havana (Cuba) at the turn of the century by Agramonte and others can be confirmed that the dengue virus is transmitted to man by the same insect vectors that transmit the virus of yellow fever

Dengue follows the geographic distribution and number of Aedes between 30 degrees north and 30 degrees south latitude In Asia, India, in Africa, the west coast and equatorial Africa, in Europe, the Mediterranean area, in America, the shores of Louisiana through Mexico, the Antilles down to Brazil Through extraordinary rapidity of invasion and the

*A different opinion has lately been expressed by A B Sabin
†Not identical with Colorado tick fever

among the first patients examined at the beginning of an epidemic a differential diagnosis is difficult between grippe (influenza) or some eruptive disease particularly measles or an attenuated form of rickettsiosis (spotted fever) The clinical syndrome of dengue appears quite characteristic to a careful observer it can be readily distinguished from other infectious endemic epidemic processes No matter what part of the body is affected in grippe or influenza including the gastrointestinal form the mucosae particularly of the respiratory tract are always invaded These are not affected in dengue On the other hand the neurotoxic symptoms of grippe are relatively *latent while in dengue these symptoms are prodromal—headache* anorexia asthenia and pyloric splanchnic spasms Last there is no "rash" in influenza as there is in the more or less diffuse form of dengue Caution is advised in dealing with children bearing in mind the possibility of many other conditions of measles particularly The fleeting character of the rash is more pronounced in dengue Signs of congestion of the mucous membranes conjunctiva etc do not occur in dengue as they do in influenza

PROGNOSIS

Prognosis is favorable except in complicated cases Death rate does not exceed 0 03 per cent (statistics of McCallum and Dwyer during the epidemic of Queensland 1927 of Blanc et al in Greece 1928, and of Calvo and others in Spain 1929) During epidemics the hematoxic and neurotoxic effects of dengue increase mortality among patients already affected by chronic disease such as tuberculosis and diseases of the liver and of the heart

Complications not only obscure the prognosis in some cases but may also *affect the differential diagnosis These are (1) gastric hemorrhage* renal complications etc at times mucocutaneous hemorrhages which on certain rare occasions (Georgopoulos 1928) reveal endothelial or vascular origin (2) ocular lesions—iritis keratitis and paralysis of the oculomotor nerve (3) changes in the nervous system particularly neuritis at times transitory psychosis with extreme asthenia, (4) cardiac changes usually functional rarely a true myocarditis

TREATMENT

Treatment is purely symptomatic It necessitates bed rest liquid diet vitamin C or orange or lemon juices Aspirin is given the first few days Antibiotics are of no avail Sulfonamides are dangerous *and should not* be administered because of the leucopenia they are not indicated from an etiologic point of view

PROPHYLAXIS

Individual prophylaxis by vaccination has been tried with doubtful results to date—an active *serum treated with bile* (Blanc and collaborators) * General prophylaxis consists of campaigns to destroy the mosquitoes that transmit the disease

*Editor's note (O F) A very promising vaccine has been described by Sabin, A. B and Schlesinger R. W

The role of *Culex fatigans* in the transmission and epidemiology of dengue has been rejected by Kligler, Aschner, Blanc, and Caminopetros (1929), and others. Transmission of the virus is not a purely mechanical function; it represents a biologic process, the conditions and phases of which are still not known. The mosquitoes are not infectious for 7 to 10 days after biting a dengue patient. The infected insect ceases to be infective when the atmospheric temperature drops to 18° C.

Blanc and Caminopetros (1928) obtained positive results of transmission by infected Aedes after a period of 84 days. These mosquitoes were kept in the laboratory at 22° C. A group of Aedes gave positive results 174 days after they had been experimentally infected. This long survival of the virus may explain, in part, the diffusion and duration of the great epidemic outbreaks, since the same mosquito can infect several persons successively (Blanc 1938).

The identity of the transmitting mosquito, when considered with the corresponding endemic foci, has suggested the probability that dengue virus is merely an attenuated virus of yellow fever. Cuban physicians at the beginning of this century, particularly Agramonte and Guiteras (1906), studied this problem with reference to the differential diagnosis of the two diseases. The more recent experiences with cross immunity, however, show that the dengue virus is capable of producing in monkeys (*Macaca mulatta* or *rhesus*) a certain degree of protective action against inoculations of the yellow fever virus (Dinger and Snijders 1931).

RESULTS OF EXPERIMENTAL INOCULATION

As to experimental inoculation of animals, we must depend exclusively upon results obtained in monkeys. In the lower animals—guinea pigs, rats, rabbits, dogs—the virus can probably be propagated without apparent symptoms, according to Kurauchi et al. (1917), Blanc and Caminopetros (1928).*

IMMUNITY

Immunity developed during dengue infection is possible, but it is variable and usually of short duration. Simmons et al. (1931), Sharp and Hollar (1935), and Blanc and Caminopetros (1930), Manoussakis and others (1931) in Greece agree in assuming that there is acquired immunity for one to four years. In endemic zones at the start of an epidemic, few natives develop the disease, but a large proportion of individuals who live away from the endemic zone, as well as newcomers to the region, become ill. Epidemic outbreaks, even when most intense, as in Greece (1928) or in Spain (1928-1929), terminate abruptly, with only a few sporadic cases remaining. This can be explained only on the basis of an immunity acquired during a mass attack. Finally, experimental observations—inoculation of virus into individuals who have recovered from dengue—point to the existence of very definite immunity.

There is no proof of the existence of any protective action in the sera of convalescents (Holt, Fleming and Kintner 1931, Manoussakis, Blanc and others). Fresh and old sera were both used; some sera were concentrated, some were administered as early as the first day of the disease, some were administered as a preventive measure—yet no protecting antibodies were found.

DIFFERENTIAL DIAGNOSIS

During epidemics, diagnosis of dengue is quite easy, because these cases present a stereotyped syndrome. With sporadic or isolated cases, or even

*Editor's note (O. K.): For mouse adaptation, see Sabin, A. B., and Schlesinger, R. W., 1945, Science, 101, 640.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis is not always easy particularly from the early stages of dengue or from influenza

TREATMENT

Treatment is purely symptomatic Absolute rest is necessary during illness and tonics during convalescence

PROPHYLAXIS

Since no vaccine is available at present prophylaxis must be limited to prevention of bite by the Phlebotomus These insects are not infectious if the atmospheric temperature drops to 54° F (18° C) according to Whittingham and others (1923) Aromatic substances such as oil of citronella keep them away They live in low damp dark places in basements behind furniture etc The upper floors of dwellings are usually free from Phlebotomus Successful campaigns against the larvae of these diptera are more difficult to carry out than against the larvae of the common mosquitoes (Anopheles Culex Aedes)

RIFT VALLEY FEVER

Rift Valley fever is a disease of sheep and newborn lambs and is transmissible to man It was discovered in 1931 in Kenya Colony (East Africa) by Daubney Hudson and Garnham (1931) and later observed by others in the Sudan and in West Africa Cases of experimental accidental infection have been observed in laboratories (Kitchen 1934, Francis and Magill 1935) one with thrombophlebitic complications terminating fatally (Schwentker and Rivers 1934)

CLINICAL SYMPTOMS

Clinical symptoms in man are similar to those of dengue although they are more acute—headache nausea vomiting chills sudden fever (39° C or more) transitory joint and muscle pains hepatic congestion subicteric tint neurotoxic signs vertigo photophobia and at times mental confusion There is also pronounced leucopenia with a tendency toward agranulocytosis Findlay (1932) Francis and Magill (1935), and others observed toxic changes in the cytoplasm and nuclei of granulocytes with persistent leucopenia during the period of convalescence

THE VIRUS

In susceptible animals the virus produces hepatitis with necrotic foci without perihepatitis and without splenomegaly although the spleen in infected sheep and lambs may show hemorrhagic foci Sometimes pericarditis as well as hemorrhagic nephritis is present

PHLEBOTOMUS FEVER (SAND FLY FEVER)

Phlebotomus fever, or sand fly fever, has been known for a long time by a variety of names—"pappataci fever," "three day fever," "dog fever," etc —in Italy and the Balkans It is an acute fever with rapid course, first studied by Doerr et al (1909) The pathogenic agent appears to be a virus transmitted to man by the bite of a small diptera of the genus Phlebotomus especially by the species *Phlebotomus pappatasii*

CLINICAL SYMPTOMS

The clinical syndrome has frequently been confused with dengue It differs in its more rapid course The fever usually lasts for 3 days, increasing to 39° to 40° C (104° F) at first There is intense reddening of the face and congestion of the conjunctiva (swollen and bloodshot eyes "dog eyes" hence the German name 'Hundskrankheit" or the English "dog disease") There is no real 'rash ' but dry skin with papules and isolated vesicles extending in many cases to the tongue palate and mucous membranes of the mouth Hypersensitivity often localized pains in various parts of the body indicates possible involvement of the nervous system in the disease Trabaud (1931) observed these nervous symptoms Jayle Mastier and Rameev (1935) described neuroretinitis in some cases, LeGac and Albrand and others (1937 1940) noted alterations of the cerebrospinal fluid—increase of pressure, albumin, and cell count These observations proved the neurotoxic action of the virus Relative bradycardia even during the short period of fever, and especially persistent leucopenia (van Rooyen and Rhodes 1940) around 3 000 to 3 500 leucocytes per cubic millimeter (on the fourth or fifth day) without anemia are characteristics in common with dengue

EPIDEMIOLOGY AND GEOGRAPHIC DISTRIBUTION

Epidemiology and geographic distribution of the disease are related to the ecology of Phlebotomus, particularly *Phlebotomus pappatasii* Shortt Endemic foci are found in the Balkans [illegible]
[illegible]

Diptera of the genus Phlebotomus are transmitters of pathogenic protozoa of the genus Leishmania These protozoa produce diseases important in tropical pathology, such as kala azar and espundia The possible relationship between sand fly fever and leishmaniasis has not been studied and is therefore unknown They are two entirely different diseases.

The virus of sand fly fever has been studied during the past few years by Kligler and Aschner (1928) by Shortt Poole and Stephens (1935) Shortt Pandit, and Rao (1939), and others It has been cultivated on the chorioallantoic membrane of the chick embryo and in tissue cultures and successfully inoculated into monkeys (Macacus) (Tedeschi and Napolitani, 1911 Shortt Poole and Stephens 1935) It remains virulent upon experimental animal inoculation Lower mammals are refractory to it Acquired immunity is brief, according to Lepine Lambert Shortt, and collaborators (1935) although McCarrison demonstrated that injection of 2 c.c. of infective blood did not produce symptoms of the disease in subjects who had recovered from an attack (Birt, 1915)

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The virus is filtrable as is that of dengue According to observations of Broom and Findlay (1933) it is about 23 to 35 millimicrons Certain species of African monkeys such as the Cebus are particularly susceptible to the virus (Findlay 1932) The virus is decidedly pathogenic for rodents (Rattus, Epymis Cricetus Microtus and others)

Protective antibodies have been found in the blood of experimentally infected animals These antibodies are able to neutralize 1 000 rat units of the virus (Schwentker and Rivers 1934) Findlay and MacCallum (1937) demonstrated a certain degree of antagonism between the virus of Rift Valley fever and the virus of yellow fever Other observers have insisted upon a possible common origin of the two viruses which cause very similar hepatic cellular lesions and which are probably transmitted by the same mosquitoes of the genus Aedes Daubney and Hudson however stated that the virus of Rift Valley fever can survive on the pupa of the tick of *Rhipicephalus appendiculatus* for 7 days without losing its virulence It may also be transmitted by direct contact (van Rooyen and Rhodes 1940)

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established by Leichtenstern (1898), who investigated several outbreaks in Cologne Prior to 1929, psittacosis was rare in England (Beddoes, 1914, and Thomson, 1929) and in the United States An outbreak in Wilkes Barre, Pennsylvania, reported by McClintock in 1917, resembled in many ways those occurring in this country during the past seventeen years The infection had doubtless been endemic in bird stores for many years but had escaped detection as a human disease Although the Paris epidemic of 1892 was caused by parrots coming from South America, only one case in 1904 has been described by Souza in Brazil.

From a relatively obscure disease, human psittacosis was suddenly raised to a malady of world wide interest in 1929 1930, when it appeared in twelve different countries and involved approximately 750 to 800 persons Careful inquiries by Roubakine (1930), by Elkeles and Barros (1931), and by Barros (1940) indicate that South American parrots were the main source of the infection and that the world wide distribution sprang from an epizootic among parrots in Brazil (for details, see Meyer, 1942). With the discovery by Meyer and Eddie in 1931 and 1932 of the prevalence of latent psittacosis in local breeding establishments and aviaries in California, observations later confirmed in Canada, Germany, Austria, Holland, and England, the endemicity and the independence of the disease from imported birds were established Evidence furnished by Meyer and Eddie, and later by Burnet, conclusively proved the existence of psittacosis in wild Australian parakeets, parrots, lorikeets, and cockatoos Canaries and finches are proved sources of human infections Later, it was further recognized that the bird to man infection chain does not depend solely on parrots and parakeets Viral agents morphologically indistinguishable from psittacosis have been demonstrated in fulmars and petrels (*Fulmar glacialis*) by Haagen and Mauer (1939), in pigeons by Coles (1941), Meyer, Eddie, and Yanamura (1942), Smadel, Wall, and Gregg (1943), and Labzoffsky (1947), in chickens by Meyer and Eddie (1942), and in Pekin ducks and sea gulls by Eddie and Meyer (1947) The infection spectrum thus far known is exceedingly broad, and spontaneous parasitism by the viral agents in many different birds and even mammals may be anticipated

It was not until the 1929 1930 pandemic that Lillie (1930) in the United States, the British microscopist Coles (1930), and Levinthal (1930) in Germany discovered the minute viral bodies in exudates, blood, and organs of human beings, birds, and experimentally infected mammals In rapid succession, Krumwiede and associates, Armstrong and McCoy in the United States, Bedson and Western in England, Levinthal in Germany, and Sacquépée in France established the disease agent as a filtrable virus, while subsequent studies by Bedson (1930), Gordon (1930), and Bedson and Bland (1932) definitely confirmed the etiologic relationship The discovery by Krumwiede, McGrath, and Oldenbusch, that the virus is readily transmitted to white mice, enabled Bedson to demonstrate the morphologic cycle in mammalian tissues Propagation of virus in embryonated eggs by Burnet and Rountree (1935), and tissue culture technics devised by Bland and Canti (1935), Lazarus and Meyer (1939), and Yanamura and Meyer (1941) furnished antigens for immunologic studies and aided development of the complement fixation test. Demonstration of the viral agent in the sputum of patients by Rivers and Berry (1932 and 1935) advanced diagnostic technics A reproducible neutralization test enabled Hilleman (1945) to differentiate the antigenic relationship of avian and mammalian psittacosis viral agents Observations on a high person to person communicability of psittacosis like agents (Louisiana outbreak, Olson and Treuting, 1944) encourages the hypothesis that nonavian, possibly human strains may play a role in the ecology of the disease (Eaton et al, 1941, Meiklejohn, et al, 1944, Smadel, 1943, and Zichis and Shaughnessy, 1945) The study of human primary pneumonia not incurred by known bacteria has in recent years led to the discovery of viral agents indistinguishable from those causing psittacosis Additional psittacosis like viruses were isolated from the respiratory tract of both apparently healthy and diseased mammals The viruses which comprise this group are listed in the current literature under the following names: Miagawanella, meningopneumonitis virus, mouse pneumonitis virus, Australian mouse pneumonitis virus, feline pneumonitis virus, San Francisco (S F), the Illinois, and the Louisiana pneumonitis viruses (Reiman 1947)

CHAPTER 20

PSITTACOSIS (ORNITHOSIS, PSITACOSIS)

KARL F MEYER

DEFINITION

Psittacosis, although primarily an avian infection, occurs sporadically and in epidemics among human beings in many parts of the world It is an acute, specific disease, characterized in the early stages by high fever and but slight physical involvement, and later by patchy pneumonitis and severe toxemia It is caused by a viral agent (*Miyagawanella psittaci*) which primarily attacks reticuloendothelial cells It is acquired by exposure to psittacine birds, pigeons, ducks, chickens, and petrels

HISTORY

The first two cases of psittacosis were described by Jurgensen (1876) At Ulster, Switzerland, in 1879, Ritter described 7 cases of a peculiar acute pneumonia with 3 deaths, the outbreak coincided with the arrival of imported sick parrots in the vicinity He reported the disease by the clinically correct and descriptive title of "pneumo typhus" but emphasized that pneumonia and typhoid were not epidemic there at the time Autopsies on the birds were negative Similar observations were made at Bern in 1882 (Ost), at Leipzig in 1886 (Wagner), and at Bonn in 1887 A large outbreak (47 cases with 13 deaths) in Paris in 1892, which followed importation of parrots from Buenos Aires, was investigated by Dujardin Beaumetz, who concluded that it was of human origin since a certain number of patients apparently had no contact with the suspected birds, many of which showed no signs of illness The following year, Dubief established con clusively that a household outbreak of 5 cases, with 3 deaths was caused by contact with an infected parrot Strong support favoring the concept of a specific infection was gained through the work of Nocard, who fatally infected a healthy parrot by placing in its cage the dried wings of parrots involved in the Paris epidemic of 1892 He also isolated from the wings a gram negative, motile bacillus, Nocard s bacillus, which Gilbert and Fournier considered etiologically related to the parrot and human diseases. This organism, known as *Bacillus psittacosis*, is indistinguishable from *Salmonella typhimurium*, and was not dem onstrated in subsequent epidemics The name "psittacosis" (from the Latin *psittacus*, a parrot) was given by A Morange in 1895 in a thesis summarizing experiences with the disease in France.

The history of the disease in countries other than France is of interest Outbreaks in Italy were traced to importations of Amazon parrots In Germany (Dohringsdorf, 1892, and Krefeld, 1899) the human disease was observed to follow exposure to parakeets or lovebirds. The most important outbreak due to this species of the parrot family occurred at Zülpich (near Cologne) in 1909, when 2 apparently healthy parakeets infected their owners, 5 nurses, and 10 visitors who had congregated at the funeral of the husband Careful bacteriologic examination of a sacrificed parakeet yielded indifferent streptococci (Bachem, Selter, and Finkler, 1910) Direct contagion from person to person, although rare, was incontestably

OF PSITTACOSIS

ISE EPIDEMICS, OCCUPATIONAL AND ACCIDENTAL INFECTION

Parrakeets

PSITTACIDAE

Miyagawanella psittaci

(Filterable)

Incubation time - 7-31 days

High temperature with slight remissions

Toxemia entirely out of proportion to physical findings

Non productive pneumonia or pneumonitis

COLUMBIDAE

Pigeon

Gould on Finch

Zebra Bird

Butterfly Finch

Java Rice Bird

Canary

GEOSPIZIDAE

Sea Gull

Chicken

Sputum — Droplet or contact

Blood virulent 1st–16th day

Sputum virulent 5th – 23rd day

Regularly in fatal cases

Autopsy, virus in lung spleen and liver

Complement fixation of serum positive 8th–15th day

INFECTED DROPPINGS

DUST AEROGENIC ROUTE

of birds in relation to incidence and importance

rimentally infected Mice, Guinea Pigs, Hamsters, ket Gophers, Rabbits, Monkeys

Fig 137—The epidemiology of psittacosis

EPIDEMIOLOGY

Geographic Distribution

Statistical data presented by Elkeles and Barros (1931), Haffenberg (1936), Barros (1940), Meyer (1943) and Meyer and Eddie (1947), although incomplete, fully attest to the worldwide distribution of psittacosis. Sporadic cases and household epidemics have been reported from Algeria, Argentina, Australia, Austria, Brazil, Canada, Czechoslovakia, Denmark, Egypt, England, France, Germany, Guatemala, Hawaiian Islands, Mexico, Netherlands, Poland, Portugal, San Salvador, Spain, Sweden, Switzerland and the United States. Excepting cases in Algeria traced to South American parrots, the disease has thus far remained unrecognized in Africa, despite at least one infection attributed to psittacine birds recently brought to England from West Africa. The mild, ambulatory or subclinical infections encountered with increasing frequency in recent years do not appear in current data but are numerous. A tabulation of official and nonofficial histories records for the period 1931-1946 in the United States 504 cases of psittacosis with *62 deaths*. During the early years of this period the majority of the infections (31 cases) were attributed to distribution and sale of locally bred and raised parakeets, but later restriction on importation of psittacine birds checked this source of infection. With the discovery of infectivity in fulmars, pigeons and chickens (1940) and more recently in ducks, several hundred human infections (186 fulmars, 103 pigeons and 5 ducks) have been traced to these birds. Epidemiologists all over the world must carefully investigate every avian and mammalian contact before inquiring into the possibility of human spreaders of virus.

Epidemic Features

The relative infrequency of human cases in Australia, Brazil, Argentina, Mexico and probably other Latin American countries, where avian psittacosis prevails among wild birds in the natural state, is not surprising in the light of newer knowledge on the natural history of the infection. The existence of epizootics among wild birds has been observed only in rare instances (Burnet and Parodi and Silvetti), since dead bodies are eaten by other animals or decompose. In birds infection originates from parents in the nest, and infected fledglings either suffer no symptoms or have overcome them by the time they are ready to fly. During the breeding period females suffer a transient activation of the infection and become shedders of the virus. This invisible cyclical spread in wild birds in the forests has little opportunity for transfer to human beings, but in domesticated birds its danger is apparent. Parrots are usually caught young, collected in depots and shipped to all parts of the world. There is ample documentation of birds becoming sick, dying and proving to be heavily infected with psittacosis a week or two after capture. Overcrowding in shipping cases, unsanitary conditions and change in climate provoke these mortalities and afford ample opportunity for spread of virus to man. Investigations on aviary bred parakeets and in pigeon lofts by Meyer and Eddie clarified the ecology of the host virus reactions. In an infected parakeet aviary, pigeon loft or zoological garden kept under the best sanitary conditions, the majority of adult birds appear healthy, although virus may be demonstrated in their spleens, livers and intestinal contents. Occasionally young birds may show signs of illness such as inactivity, loss of appetite, soiling of the vent and nasal discharge; a variable proportion may die. Overcrowding, overbreeding, uncleanliness and lack of care upset the balanced

is probably due to prolonged and frequent contact with infected birds in the closed rooms of a winter household. *It is well to emphasize, however, that* severe psittacosis on the Faroe Islands and among pigeon fanciers is not uncommon in midsummer and early fall. Observations indicate that the disease can be contracted throughout the year (Meyer, 1942).

Age, Sex, Race, and Occupation.—People of middle age, rarely children, are involved in the single or multiple case infections which develop in the same household. With the aid of the complement fixation test, Meyer and Eddie (1947) detected 15 juvenile cases of mild pneumonitis in a group of 111 persons handling pigeons, chickens, and parrots who gave positive reactions in diagnostically *significant titers*. *Thus while disposition is not confined to* older age groups, the likelihood of contracting the disease increases with age. The recent isolation of a psittacosis virus from the lung of a 14-year-old boy who handled birds further attests to the susceptibility of younger age groups.

There is a greater incidence of psittacosis in women than in men. The heavier distribution in women is ascribable to propinquity, that is, more women than men raise parakeets commercially or keep them as pets. Where the interest in the bird raising business has shifted to males, the likelihood *of infection and high case fatality rate are well documented. In the outbreak* at Cordoba, Spain, which followed auctioning of highly infected birds by male traders and barterers, the ratio of males to females was 49:36 (Barros). That occupational psittacosis is quite common in persons engaged in the breeding, raising, care, transportation, and sale of psittacine birds, pigeons, and ducks has not been accepted by all, although published records amply attest to its existence (Meyer, 1942 and 1943). The apparent immunity of men and women *continuously exposed to heavily infected parakeets, parrots, or pigeons* is in part attributable to subclinical infections. Limited serologic surveys among employees in aviaries, pigeon lofts, and zoological gardens lend support to this interpretation of epidemiologic observations. A survey of 110 cases in California revealed that 45, or nearly 40 per cent, were owners of parakeet aviaries or pigeon lofts, or that members of their families were. *During the* height of experimental investigations of psittacosis in 1929 and 1930, 38 laboratory infections were *contracted. Despite the institution of precautionary* measures, an additional 17 cases with 2 deaths have occurred in Germany, Argentina, and the United States since 1934.

Human Case to Case Infection.—Older observations and new reports show the increasing frequency of human case to case infections. In at least 23 instances involving 30 nurses, contact with sick birds was definitely excluded. Twice repeated human to human passage has been seen by Haagen and Kruckeberg (1937), and a chain transmission *in the third generation* has been reported by Hamre. A physician contracted the disease from a fatal case and was visited by an intern who developed psittacosis and recovered, but who, while ill, infected his nurse, who died; she in turn had transmitted the virus to a second nurse. More disconcerting are the transmissions which have oc-

immunity in the individual birds and favor epizootics Enormous masses of virus are dispersed by sick and dying birds providing a means of spread to owners ultimate purchasers or other contacts How long psittacine birds or pigeons are infective is not definitely known but epidemiologic and laboratory observations leave little doubt that they may carry or intermittently shed virus for years

Fleeting or prolonged exposure in a room house pet store aviary breeding establishment pigeon loft or barnyard where visibly diseased or apparently healthy parrots parakeets canaries pigeons ducks or chickens are kept may result in human infections Usually the responsible birds have been recently acquired In the past single cases escaped detection and the reports deal principally with the well known house epidemics which gave the epidemiology of psittacosis its characteristic stereotyped pattern Apart from its epidemiologic interest this feature of the disease is of diagnostic value especially in differentiating psittacosis from influenza which is more pandemic and rarely appears in localized outbreaks The handling of feathers from parrots or the cleaning of dead fulmars pigeons chickens and ducks have been responsible for infections Removal of manure from pigeon lofts is not infrequently followed by human psittacosis

Mode of Transmission

The mode of transmission of the avian virus to man is manifold (1) Direct contact with the diseased birds or objects fouled by excreta is the most common mode of transmission (2) Indirect transfer by air played an important role in the Zulpich epidemic in the cases reported by Horder and Gow (1930) and in the outbreak at the National Institute of Health (McCoy 1931) (3) Bite wounds may initiate infection (Faulscher et al 1945) The dispersion of the viral agent adherent to *desiccated fecal droppings may be* readily demonstrated in sentinel experiments with Java sparrows as advocated by Meyer (1942) Furthermore the ease with which inhalation of virus induces pneumonic lesions in susceptible mammals amply attests to the respiratory tract as the principal portal of entry for the virus Finally the main burden of infection in human cases falls on the respiratory tract lobular distribution of the pneumonic consolidation and inflammation of the mucosa of the upper respiratory tract are constant features of cases that come to autopsy

DISTRIBUTION AND PREVALENCE

Distribution is world wide Statistical data however must be considered approximations which deal with frank clinical cases No attempt has been made to secure information concerning the subclinical or mild cases often suspected but only occasionally proved serologically which have been encountered with increasing frequency in recent years

Seasonal Incidence The great epidemics of the past occurred during the winter and in Germany and Argentina the predominance of the disease at that time of the year (January to April) is striking The phenomenon

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curred in hospitals. In an epidemic in Buenos Aires reported by Loizaga and Averbach (1945), interhuman contagion was a striking feature of the outbreak, extending at times to the third passage. The experience detailed by Eaton, Beck, and Pearson (1941) illustrates the infectiousness of a man who transmitted psittacosis to 3 nurses. The 1943 epidemic of a severe pneumonitis in the Bayou region of Louisiana in which there were 8 deaths in 19 recognized infections among nursing attendants late (48 hours before death) in the illness of fatal cases, emphasizes the importance of direct contact in human to human transmission (Treuting and Olson 1944). Statistics such as these should serve to remind physicians that the occupational hazard to themselves and to nurses is considerable.

ETIOLOGY

The Causative Organism

The infective agent of psittacosis in birds and man is an obligatory intracellular parasite. It is specific and forms particulate elementary bodies. The agent develops in the cytoplasm of the reticuloendothelial cells in tissue cultures of mesenchyme cells in fibroblasts, and in epidermis epithelial and liver cells or cells derived from all three embryonic layers (Yanamura and Meyer 1941). On the basis of morphologic and antigenic similarities, psittacosis agents and those of lymphogranuloma venereum of man and of mouse and feline pneumonitis have been placed in a group intermediate between the rickettsiae and the true filtrable viruses.

The viral agent common to the group is an infective spherical or hemispherical—not rod shaped—elementary body tinctorially demonstrable with basic dyes. The infective bodies are usually 300 to 450 millimicrons in size and are held back partially or completely by the usual filters. They are readily propagated in the yolk sac of the embryonated hen's egg and in tissue cultures. They are agglutinated by specific antisera and serve as antigens in diagnostic complement fixation tests. They generate protective antibodies in birds and mammals including man. Moshkovsky (1945) has suggested the name *Miyagawanella psittaci* for the agent and has grouped it in the family of the Chlamydozoaceae.

Morphology and Staining Reactions

In microscopic preparations thin films made from plastic exudates and stained with Giemsa solution or preferably according to the method of Macchiavello the elementary bodies appear as purplish dark red or blue spherical structures singly or in pairs. In tissue cultures or in material from yolk sacs they increase rapidly in size and become embedded in a homogeneous ground substance or matrix. These initial bodies at first divide into elements of comparable size but as multiplication progresses the elements of division become smaller and smaller until the final elementary body stage is reached (Bland and Canti, 1935). Yanamura and Meyer (1941) *by relating morphologic findings in films and sections to the intervals* of the dynamic time sequence in tissue cultures established the following cycle of development.

One or more elementary bodies which are red when tinged according to Macchiavello or black purple according to Castañeda invade a cell and incite (if the cell is healthy) the formation of a single common matrix. If the virus particles disperse at opposite ends of a cell, each group may be surrounded by a separate matrix thus inducing double or triple infection foci within one cell. These forms correspond to the "plaques" of Bland and Canti, or to the "inclusion bodies" of Levinthal. The matrix of the homogeneous inclusion bodies stains blue green according to Macchiavello and since it is not densely colored the early virus particles are readily identified in increasing numbers. These large forms, measuring 2 to 12 microns

appear 18 to 24 hours after infection As the matrix becomes less dense, tinctorial differences become apparent *The larger virus particles are stained blue*, while the smaller forms (0 3 to 0 4 micron) are red

Electron photographs suggest that the elementary bodies contain a large amount of water and show two components a dense substance, usually *centrally located*, and a thinner, surrounding substance, which *appears to represent a limiting membrane from which the* central mass retracts (Hamre, Rake, and Rake 1947)

Some elementary bodies have a sticky substance on their surfaces, and it is not unlikely that this is responsible *for the different tinctorial reactions* *In living preparations, the* initial particles immobile in the originally rigid homogeneous inclusion bodies, increase in motility until finally in the flexible virus colony they undergo rapid oscillatory (Brownian) movement *This change more or less coincides with the conversion from blue to red staining* reactions The inclusion body is always surrounded by a definite membrane which persists even when in multiple infections one or two colonies coalesce Free dispersal of the elements *of a colony through the cytoplasm is rarely observed.*

At the forty eighth hour the matrix of the inclusion body presents evidences of liquefaction By that time, the elementary bodies which stain deeply red in Macchiavello preparations *have become so numerous that they may pack the cytoplasm* *Death of the host cell and* autolysis of the colony releases myriads of particulate elementary bodies, which are capable of invading and repeating the cycle in new cells

Levinthal s observation, that in damaged cells the virus multiplies without a definite matrix formation, is readily demonstrated in agar tissue cultures in which the embryonic cells are merely in a state of functional survival The time required for completion of the *developmental cycle is much shorter* *Large and small elementary bodies divide and multiply* to enormous numbers in the cytoplasm of highly vacuolated cells In prepartions stained by the Giemsa method the membrane is quite distinct, although no matrix can be demonstrated. *Filtration tests (Lazarus and Meyer, 1939) through collodion membranes and recent* electron micrographs by Kurotchkin et al (1947) established the mean diameter of the elementary bodies as 455 mμ ± 78 mμ The size of the feline pneumonitis virus in gold shadowed preparations *is reported as 525 mμ ± 84 mμ* (Hamre et al, 1947)

The initial bodies in the plaques are always larger than the parent organisms and, according to Bedson and Bland, are low in virulence, since they apparently encounter difficulties *in entering into cells* That the cytoplasmic plaques or inclusion bodies are true virus colonies made up of elementary bodies is conclusively established Merely the exact nature of the matrix remains uncertain Although findings in tissue cultures strongly incriminate it *as a product of the cytoplasm*, it is recalled that Findlay (1938) suggested that it may conceivably originate as a secretory product from the elementary bodies

Cultivation and Propagation

Psittacosis viruses are readily grown in media of the Maitland, La Rivers, and the Zinsser Fitzpatrick Wei agar tissue types (Yanamura and Meyer, 1941) More recently the roller tube tissue technic has come into use (Morgan and Wiseman, 1946) Chorio allantoic, amniotic, allantoic, and yolk inoculations in chick embryos are continuously employed for the preparation of highly infective suspensions which are used for serologic and immunologic studies and routine examinations (*for details, consult Beveridge and Burnet, 1946*)

Resistance to Physical and Chemical Environment

Prolonged centrifugation—6 to 8 hours—at 15 000 r p m has been shown to deposit the major portion of the virus Exposure to 56° C for 30 minutes does not completely destroy virus in mammalian organs Chick embryo virus is readily inactivated at 60° C for 10 minutes Crude heavy suspensions in broth may remain infectious at ±4° C for several weeks, but preparations of elementary bodies in buffered saline are noninfectious 29 days after preparation and storage Frozen at −70° C, the virus remains active for over 2 years

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Cultivation and Propagation

Psittacosis viruses are readily grown in media of the Maitland, Li Rivers and the Zinsser Fitzpatrick Wei agar tissue types (Yanamura and Meyer, 1941) More recently the roller tube tissue technic has come into use (Morgan and Wiseman 1946) Chorio allantoic amniotic, allantoic and yolk inoculations in chick embryos are continuously employed for the preparation of highly infective suspensions which are used for serologic and immunologic studies and routine examinations (for details, consult Beveridge and Burnet 1946)

Resistance to Physical and Chemical Environment

Prolonged centrifugation—6 to 8 hours—at 15,000 r.p.m has been shown to deposit the major portion of the virus Exposure to 56° C for 30 minutes does not completely destroy virus in mammalian organs Chick embryo virus is readily inactivated at 60° C for 10 minutes. Crude heavy suspensions in broth may remain infectious at +4° C for several weeks, but preparations of elementary bodies in buffered saline are noninfectious 29 days after preparation and storage Frozen at -70° C, the virus remains active for over 2 years

In 50 per cent glycerin in buffered saline at pH 7 6 and at ±4° C., heavy suspensions retain their activity for 10 to 20 days Sputums and human lung specimens rapidly lose their potency in glycerin Formalin, 0 1 per cent, and phenol, 0 5 per cent, in activate the psittacosis virus in 24 to 36 hours, while 10 per cent ether at room temperature destroys it within 30 minutes on heavy chick embryo suspensions or in agar tissue cultures

Toxin

According to Rake and Jones (1944), yolk sacs infected with the meningopneumonitis virus of Francis and Magill and shaken with amniotic and allantoic fluid are toxic to mice on intravenous or intraperitoneal injection This toxin is labile and is not readily separated from the elementary bodies Specific antitoxins produced in rabbits and chickens are ef fective against a few lethal doses of it Many of the lesions observed in animals infected with the Louisiana virus bear signs of toxemia.

Virulence

Psittacosis viruses isolated from different species of animals, and from man, vary con siderably in their effects on mice Strains of proved pigeon or duck origin produce irregu lar mortalities in white mice on intraperitoneal inoculation. It is claimed that some strains which are adapted to human beings lose their pathogenicity for mice and birds, latent in fections are demonstrable only up to 21 days by subinoculation (Meiklejohn et al, 1944)

Antigenic Structure

In 1936, Bedson found that psittacosis virus, which he used as a reagent in the comple ment fixation test, contained at least two important antigens one, heat labile, was destroyed by temperatures above 60° C, while the other could withstand boiling As a result of infec tion, antibodies to both antigens are produced, the latter in considerably greater quantity Although the role of the antibodies to heat stable antigens in immunity to psittacosis serum is not known, they constitute a reliable index of infection The heat stable antigen is also ether soluble, and in all probability is common to the protein molecule of all viruses in the lymphogranuloma psittacosis group Infected yolk sacs or mouse spleen suspensions treated with phenol, then boiled and centrifuged, yield clear supernatant fluids, which produce al lergic reactions in sensitized guinea pigs and suggestive precipitin reactions with specific antisera. Nothing definite is known about the antigens, which give rise to species specific antibodies responsible for the highly specific protection against different members of the lymphogranuloma psittacosis group, or of the neutralization of toxins (Hilleman, 1945)

Distribution in the Body and Routes of Escape

Through inoculations of parakeets (Bedson, 1930) and mice (Eddie and Meyer, 1947), blood from patients tested during the first two weeks of the disease has been repeatedly found to contain the virus It was Coles (1930 who first observed elementary bodies in sera from pa tients Sputum (up to and including the twenty sixth day) and occasionally throat gargling and vomitus may yield the infective agent in animal tests At autopsy, virus is readily de monstrable in the pleural exudates, pneumonic lesions, spleens, and livers of human beings It has been regularly isolated in exudates, blood, livers, spleens, kidneys, intestinal and cloacal contents, and urine from parrots, pigeons, and ducks The virus escapes from the body of birds and mice via the intestinal and nasal discharges. In latent infection of birds, virus is confined to the spleen and liver, irregularly to the intestinal contents Numerous investigators have seen viral bodies in man in the epithelial lining of the pulmonary alveoli, in the liver, the Kupffer cells, and in macrophage cells of splenic sinuses With the aid of the differential staining method of Noble, which reveals red elementary bodies against a green background, viral elements are readily seen in nearly every organ of animals and birds dead of psittacosis.

SUSCEPTIBLE ANIMALS

(1) Mammals

For the isolation of the virus, the mouse may be infected by the intraperitoneal, intravenous, subcutaneous, intranasal, and intracerebral routes and by feeding. Death may occur in 3 to 30 days, with an average of 6 to 10 days. Some mice will recover or latent infection may persist for 10 to 12 months (Meyer and Eddie, 1933, and Bedson, 1938). When death has occurred 2 to 4 days after inoculation, autopsy shows the abdominal viscera covered by a thin sticky exudate, *with endothelial cells and leucocytes packed with elementary bodies.* When death occurs 10 to 20 days after inoculation, the viscera are coated with a thick layer of film; the enlarged liver shows marginal necrosis, and the spleen is voluminous and soft. Mice with latent infections have enlarged spleens. Psittacosis virus administered intranasally produces widespread consolidation of either lobe of the lung. Discrete, grayish foci of pneumonia are manifested as the limiting infective dilutions of virus are approached (Rake and Burnet, 1941 and Hornus 1940).

With the exception of *feline strains* and certain murine strains (Grebb), most psittacosis viral agents injected intracerebrally cause irritability, motor hyperactivity, ataxia, convulsive seizure, and death within 3 to 6 days. Microscopically, the meningoencephalitis is characterized by an exudate of polymorphonuclear and mononuclear cells, which extends along the blood vessels into the brain. The cellular elements are usually very rich in viral bodies (Gordon, 1930, Rivers and Berry, 1931). In the *feeding* experiments reported by Fortner and Pfaffenberg (1934), a high percentage (78 per cent) of the mice succumbed to abdominal psittacosis, in 17 of 46 cadavers, pneumonic lesions were also found. Ingestion is apparently associated with inhalation of the virus.

Most strains of psittacosis are reported to have little visible effect on guinea pigs when inoculated intraperitoneally. They incite a prolonged febrile reaction. However, strains recently isolated in Louisiana (Olson and Larson, 1944-1945, Fite, Larson, and Olson, 1946) and California from human cases of pneumonitis are highly virulent for guinea pigs irrespective of inoculation routes. The intensity of the clinical illness depends on the dose given; anorexia, fever, listlessness, and loss of weight are followed by death within 4 to 10 days.

Some strains produce fatal meningoencephalitis in *rabbits* infected by the intracerebral route. *Pulmonary focal infiltrations and extensive pneumonic consolidations*, occasionally fatal, may be produced by intratracheal injection of virus (Rivers and Berry, 1931, and Morgan, 1946).

Monkeys are susceptible to intratracheal and intracerebral inoculations while intraperitoneal injections may produce no ill effects (Olson and Larson, 1945). Pocket gophers *(Thomomys bottae bottae)*, Syrian hamsters *(Cricetus auratus)*, cotton rats *(Sigmodon hispidus)*, and squirrels *(Citellus beecheyi)* are successfully infected by intranasal and intracranial routes.

(2) Birds

Reports from Australia and Argentina indicate that spontaneous psittacosis is common *among wild parrots, parakeets, and conures*, probably as a population regulator. At least 33 different species of the parrot family are known to be hosts to the virus. Common to all is a high incidence of prolonged latent infection, which is frequently responsible *for introducing the disease to finches and canaries in bird shops* and aviaries. High mortalities in importations (Meyer and Eddie, 1939, and Dunnahoo and Hampton, 1945) or outbreaks in zoological gardens (Burnet, 1935, Troup, Adam, and Bedson, 1939, and Tomlinson, 1941) follow crowding in unsanitary cages or exposure to low temperature, which induces relapses in latent infections. Enormous virus dispersal rapidly spreads the infection from diseased to susceptible birds. A variable number may die but a great many carriers develop.

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The clinical disease in different species of parrots, parakeets or conures infected with psittacosis virus is not characteristic. Autopsies and laboratory examinations are imperative to prove the nature of the disease. Far reaching is the discovery that visibly "healthy" birds harbor the virus and as shedders, disseminate the organisms. Psittacosis among finches in the wild has not been reported. Canaries as well as finches are aberrant hosts which acquire infection, as a rule, from exposure to diseased parakeets or parrots or through seeds contaminated by droppings of these species (see Meyer 1942).

The observations of Coles (1940), Meyer et al (1942), Smadel et al (1943 and 1945), Andrewes and Mills (1943) and [illegible]alzoffsky (1947) prove a wide distribution of psittacosis in the *pigeon* lofts of the United States, Canada, South Africa and Great Britain. Complement fixation tests seem to indicate that the majority of the birds are infected as squabs, and latency of the virus may be demonstrated in at least 10 to 20 per cent of the pigeons. Relatively few acute, spontaneous infections uncomplicated by salmonellosis or by other viruses have been studied, however, epizootics have been described (Smadel et al.). *Chickens (Gallus gallus)* have been found to carry virus in their organs and cloacal contents when in contact with pigeons (see Meyer 1943). Recent studies by Eddie and Meyer have proved the existence of acute and chronic psittacosis among *Pekin ducks* (Anasplatyrhynchos) commercially bred and raised in California and on Long Island. Extent of the disease in fulmars or petrels *(Fulmar glacialis)* on the Faroe Islands and in Iceland is unknown (Haagen and Mauer, 1939, and Bedson, 1940). Parakeets *(Melopsittacus undulatus)*, Amazon parrots *(Amazona festiva, Amazona aestiva)*, parrotlets *(Forpus passerinus)*, African lovebirds *(Agapornis personata)*, and green paroquets *(Myiopsitta monachus)* readily acquire psittacosis by exposure in cages or by inoculation. Loss of weight, weakness, watery stools, and nasal discharges are observed during the course of the disease, which in a fair percentage may not be fatal. Autopsy findings reveal a seropurulent coating on the walls of the air sac and the inner lining of the sternum. The liver is usually swollen, pale saffron to ocher colored, occasionally studded with small and large necrotic areas. The spleen is usually enlarged and sometimes spotted with fine necroses. The kidneys are swollen, grayish and soft. Only in rare instances are lesions demonstrable in the lung. In chronic infections the gross lesions are essentially negative except for a definitely enlarged spleen, thickening of the air sacs and scars of healed necroses in the liver. Ricebirds *(Munia oryzivora)*, canaries *(Serinus canaria)*, sparrows *(Zonotrichia and Passer domesticus)* and various finches *(Carpodacus mexicanus* [illegible] and *(*[illegible]*)* may be fatally infected by inoculation or exposure.

TRANSMISSION

Since no intermediate hosts and vectors have been established, the mode of virus transmission from bird to bird and from bird to man is relatively simple. Inhalation and, in aviaries, ingestion play the principal roles.

IMMUNITY

Individuals recovering from an attack of psittacosis are generally believed to be resistant to reinfection. Records of second infections are not numerous, but when the total experience with the disease is taken into consideration they are significant. Rasmussen (1938) reported two women patients who contracted the fulmar disease a second time. Wenckebach (1936) and Meyer (1939, 1940) have records of proved second attacks which may be interpreted as relapsing cases or as reinfection. Apparently the immunity is not absolute, and the residual virus held in certain tissues is not always in an innocuous equilibrium.

Another problem deserves consideration in connection with immunity to psittacosis. Persons who come in contact repeatedly with infected birds may

develop subclinical forms of the disease and possibly act as transient human carriers of infection (Gerlach, 1936).

Finally, a viral agent endowed with persistence in the tissues occasionally produces a chronic *carrier stage after recovery*. A patient who is still shedding virus in the sputum eight years after a severe psittacosis infection has recently been discovered by Meyer and Eddie (1947). Parrots, parakeets, pigeons, mice, guinea pigs, rabbits and monkeys which recover from one attack of psittacosis are usually resistant to a second inoculation.

To what extent immunity is dependent on latent infection has not been determined. Observations by Yanamura and Meyer (1942) on mice and Eddie and Meyer on monkeys and pigeons amply attest to the fact that immunity of the nonsterile type fails to operate when a relatively large superinfection is administered by the intracerebral or intranasal route. On the other hand it is equally well known *that guinea pigs which have recovered from an infection* and with organs free from psittacosis virus resist reinfection with massive doses of Louisiana virus. The ability of mice to acquire immunity and resist artificial infection is apparently determined by the genetic constitutions of individual animals. Following a relatively mild infection, some individuals acquire a low grade immunity protective against frank disease but not against persistent latent infection, while others develop an immunity which enables them to resist infection by destroying a dose of virus not exceeding 100 M.L.D. (*Yanamura and Meyer, 1941*). *Is it therefore not reasonable to consider that* the immunity of human beings recovered from psittacosis is in part dependent on genetic factors and on the relative dose of the viral agent to which they are exposed on reinfection?

Active immunity against psittacosis has been produced in mice by repeated inoculation *of viral suspensions inactivated by methylene blue or 0.2 per cent formalin. A considerable* degree of immunity has been conferred to rice birds and parakeets with formalin treated noninfective tissue culture antigens. Monkeys, guinea pigs, mice, rabbits and chickens have been *hyperimmunized with live virus; their sera have been found* to contain complement fixing, protective, and toxin neutralizing antibodies (see Hilleman, 1945). Immunizations of human volunteers against psittacosis have been carried out with dilutions of live virus subcutaneously administered (Rivers and Schwentker, 1934). Suspensions of infected mouse livers and spleens diluted 1:1,000 to 1:10, respectively, were given intramuscularly in 0.5 c.c. amounts in increasing concentrations at weekly intervals. No ill effects were observed and the sera were later shown to have developed neutralizing antibodies. The injection of antigens prepared from phenol killed, ether extracted yolk sac suspensions, if administered repeatedly in large amounts, likewise stimulates the production of antibodies in man. Antigens prepared from infected yolk sacs lyophilized before extraction and rich in elementary bodies protected 75 per cent of mice *following three abdominal injections against 1 to 10* M.L.D. by the respiratory or the intracerebral route (Wagner et al., 1946). Early reports on the question emphasized that neutralizing antibodies could not be demonstrated in the sera of convalescent cases of psittacosis. *By using a more delicate technic*, however, Rivers and Schwentker (1934) found that monkeys recovered from psittacosis pneumonia or vaccinated with live virus possessed neutralizing antibodies in their sera, but the titer was relatively low. *Some human beings with positive histories of psittacosis* possessed demonstrable neutralizing antibodies. Similar observations were made by Meyer and Eddie (1939) on sera from human patients, guinea pigs and birds hyperimmunized with live virus.

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[illegible]

The neutralization test, while not too reliable for diagnosing psittacosis, has, in the hands of Hilleman (1945), proved invaluable in the identification of members of the lymphogranuloma psittacosis group By intraperitoneal inoculation of chickens or rabbits, he prepared neutralizing antisera of relatively high titer and sharp specificity Serum virus mixtures are tested by intranasal or intracerebral inoculation of mice By means of cross serum neutralization tests, Hilleman, and, more recently, St John and Gordon (1947), observed that the pigeon pneumonitis and meningopneumonitis viruses of Francis and Magill are similar to each other and different from other agents of the group Mouse pneumonitis viruses proved to be similar, but different from all other agents The lymphogranuloma virus was found to differ from all other agents thus far tested. The protective effect of antisera on experimental infections has also been demonstrated by these tests

As early as 1930, Bedson had shown that the sera of psittacosis patients react specifically in *complement fixation tests* when brought in contact with infectious mouse spleen Improvements in antigen preparation by Bedson (1935 and 1936), Meyer and Eddie (1939), and Smadel, Wertman, and Reagan (1943) lead to the demonstration of complement fixing antibodies as early as the tenth day of the patient s illness, with increasing titers during convalescence Parrots and parakeets (Meyer and Eddie, 1939), recovered from psittacosis, develop antibodies that fix complement with psittacosis and lymphogranuloma antigens The sera of pigeons (Eddie and Francis, 1942) react only in the presence of psittacosis antigens In the course of active immunizations with live or dead virus, specific complement fixing antibodies are demonstrable in the sera of mice, guinea pigs, rabbits, and monkeys The complement fixation test is a useful aid in the survey of shipments of imported psittacine birds and flocks of pigeons Antibodies are present in the majority of these birds when in a latent state of infection, it is therefore the best tool for the quick survey of sources of infection

Bedson (1933), Lazarus and Meyer (1939), Hilleman (1943), and Labzoffsky (1946) have shown that the hyperimmune sera of guinea pigs, rabbits monkeys, and chickens *agglutinate* purified suspensions of elementary bodies in titers as high as 1 320 Agglutinins are, in fact, the only antibodies which besides protective properties, may be demonstrated in the sera of hyperimmune chickens and ducks Convalescent sera obtained from human beings contain agglutinins in diagnostically significant titers Studies by Meyer (1941) implicated phagocytic activity, possibly aided by humoral antibodies in the immunity process Heat stable psittacosis antigens produce definite *allergic cutaneous reactions* in guinea pigs, and occasionally in man (Wilches et al, 1946) Frei antigen fails to incite typical skin reactions in patients recovered from psittacosis or in carriers Antigens prepared from yolk sacs infected with meningopneumonitis or psittacosis virus produced skin reactions—erythema and induration—when injected intradermally into rabbits convalescent from respiratory meningopneumonitis infections (Morgan, 1947)

PATHOLOGY

The changes found at autopsy are those of a general septicemia with inflammatory processes in the lungs Detailed pathologic data may be found in Haedke (1898), Leichtenstern (1899), Oberndorfer (1930), Hutchinson, Rowlands, and Simpson (1930), Maclachlan Permar, and Rogers (1930), Peterson et al (1930), Sturdee and Scott (1930), Bortz and Green (1930), Scholte (1930), Polayes and Lederer (1932), Lillie (1933), Foord (1934), Mansens (1934), Haagen and Kruckeberg (1937), Barros (1940), Binford and Hauser (1944), and Tanner et al (1945) This mass of literature emphasizes the following findings

Lungs—The consolidated areas are readily palpable and are sharply demarcated from normal lung tissues They appear as gray or gray reddish,

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Finally, a viral agent endowed with persistence in the tissues occasionally produces a chronic carrier stage after recovery A patient who is still shedding virus in the sputum eight years after a severe psittacosis infection has recently been discovered by Meyer and Eddie (1947) Parrots parakeets pigeons, mice, guinea pigs rabbits, and monkeys which recover from one attack of psittacosis are usually resistant to a second inoculation

To what extent immunity is dependent on latent infection has not been determined Observations by Yanamura and Meyer (1942) on mice and Eddie and Meyer on monkeys and pigeons amply attest to the fact that immunity of the nonsterile type fails to operate when a relatively large superinfection is administered by the intracerebral or intranasal route On the other hand it is equally well known that guinea pigs which have recovered from an infection, and with organs free from psittacosis virus, resist reinfection with massive doses of Louisiana virus The ability of mice to acquire immunity and resist artificial infection is apparently determined by the genetic constitutions of individual animals Following a relatively mild infection some individuals acquire a low grade immunity protective against frank disease, but not against persistent latent infection while others develop an immunity which enables them to resist infection by destroying a dose of virus not exceeding 100 M L D (Yanamura and Meyer, 1941) Is it therefore not reasonable to consider that the immunity of human beings recovered from psittacosis is in part dependent on genetic factors and on the relative dose of the viral agent to which they are exposed on reinfection?

Active immunity against psittacosis has been produced in mice by repeated inoculation of viral suspensions inactivated by methylene blue or 0 ° per cent formalin A considerable degree of immunity has been conferred to ricebirds and parakeets with formalin treated noninfective tissue culture antigens Monkeys guinea pigs mice rabbits, and chickens have been hyperimmunized with live virus, their sera have been found to contain complement fixing, protective and toxin neutralizing antibodies (see Hilleman, 1945) Immunizations of human volunteers against psittacosis have been carried out with dilutions of live virus subcutaneously administered (Rivers and Schwentker, 1934) Suspensions of infected mouse livers and spleens diluted 1 1 000 to 1 10 respectively, were given intramuscularly in 0 5 c c amounts in increasing concentrations at weekly intervals No ill effects were observed, and the sera were later shown to have developed neutralizing antibodies. The injection of antigens prepared from phenol killed ether extracted yolk sac suspensions if administered repeatedly in large amounts, likewise stimulates the production of antibodies in man Antigens prepared from infected yolk sacs lyophilized before extraction and rich in elementary bodies protected 75 per cent of mice following three abdominal injections against 1 to 10 M L D by the respiratory or the intracerebral route (Wagner et al 1946) Early reports on the question emphasized that neutralizing antibodies could not be demonstrated in the sera of convalescent cases of psittacosis By using a more delicate technic, however, Rivers and Schwentker (1934) found that monkeys recovered from psittacosis pneumonia or vaccinated with live virus possessed neutralizing antibodies in their sera, but the titer was relatively low Some human beings with positive histories of psittacosis possessed demonstrable neutralizing antibodies Similar observations were made by Meyer and Eddie (1939) on sera from human patients guinea pigs, and birds hyperimmunized with live virus

The neutralization test, while not too reliable for diagnosing psittacosis, has, in the hands of Hilleman (1945), proved invaluable in the identification of members of the lymphogranuloma psittacosis group By intraperitoneal inoculation of chickens or rabbits, he prepared neutralizing antisera of relatively high titer and sharp specificity Serum virus mixtures are tested by intranasal or intracerebral inoculation of mice By means of cross serum neutralization tests Hilleman and, more recently, St John and Gordon (1947), observed that the pigeon pneumonitis and meningopneumonitis viruses of Francis and Magill are similar to each other and different from other agents of the group Mouse pneumonitis viruses proved to be similar, but different from all other agents The lymphogranuloma virus was found to differ from all other agents thus far tested The protective effect of antisera on experimental infections has also been demonstrated by these tests

As early as 1930, Bedson had shown that the sera of psittacosis patients react specifically in *complement fixation tests* when brought in contact with infectious mouse spleen Improvements in antigen preparation by Bedson (1935 and 1936) Meyer and Eddie (1939), and Smadel, Wertman, and Reagan (1943) lead to the demonstration of complement fixing antibodies as early as the tenth day of the patient s illness with increasing titers during convalescence Parrots and parakeets (Meyer and Eddie 1939) recovered from psittacosis, develop antibodies that fix complement with psittacosis and lymphogranuloma antigens The sera of pigeons (Eddie and Francis, 1942) react only in the presence of psittacosis antigens In the course of active immunizations with live or dead virus, specific complement fixing antibodies are demonstrable in the sera of mice guinea pigs rabbits and monkeys The complement fixation test is a useful aid in the survey of shipments of imported psittacine birds and flocks of pigeons Antibodies are present in the majority of these birds when in a latent state of infection, it is therefore the best tool for the quick survey of sources of infection

Bedson (1933) Lazarus and Meyer (1939) Hilleman (1943) and Labzoffsky (1946) have shown that the hyperimmune sera of guinea pigs rabbits, monkeys, and chickens *agglutinate* purified suspensions of elementary bodies in titers as high as 1 320 Agglutinins are, in fact, the only antibodies which besides protective properties, may be demonstrated in the sera of hyperimmune chickens and ducks Convalescent sera obtained from human beings contain agglutinins in diagnostically significant titers Studies by Meyer (1941) implicated phagocytic activity, possibly aided by humoral antibodies, in the immunity process Heat stable psittacosis antigens produce definite *allergic cutaneous reactions* in guinea pigs, and occasionally in man (Vilches et al, 1946) Free antigen fails to incite typical skin reactions in patients recovered from psittacosis or in carriers Antigens prepared from yolk sacs infected with meningopneumonitis or psittacosis virus produced skin reactions—erythema and induration—when injected intradermally into rabbits convalescent from respiratory meningopneumonitis infections (Morgan 1947)

PATHOLOGY

The changes found at autopsy are those of a general septicemia with inflammatory processes in the lungs Detailed pathologic data may be found in Haedke (1898) Leichtenstern (1899) Oberndorfer (1930), Hutchinson, Rowlands and Simpson (1930) Maclachlan Permar and Rogers (1930), Peterson et al (1930), Sturdee and Scott (1930), Bortz and Green (1930), Scholte (1930) Polayes and Lederer (1932), Lillie (1933), Foord (1934), Mansens (1934), Haagen and Kruekeberg (1937), Barros (1940), Binford and Hauser (1944), and Tanner et al (1945) This mass of literature emphasizes the following findings

Lungs—The consolidated areas are readily palpable and are sharply demarcated from normal lung tissues They appear as gray or gray-reddish,

sometimes as purplish or plum colored (*Binford and Hauser*) lesions without compensatory emphysema On section they are smooth moist glistening or of dry granular appearance The pleura may be glistening or exhibit petechiae and fine fresh fibrin deposits The trachea and bronchi may contain a small amount of serous mucoid fluid in the majority of cases they are empty and the mucosa is not swollen When the psittacotic process is complicated by secondary terminal bacterial invasion the bronchi are distended and filled with purulent exudate Tracheobronchial lymph nodes may be enlarged Microscopic examination invariably discloses that areas which grossly appeared to be completely consolidated consist of lobular changes not evenly distributed throughout the tissues Alveoli containing air or serum are dispersed through the consolidated portion of the lung substance Exudates in the alveoli are irregularly distributed and uneven in character The early lesions consist of outpourings of fluid into alveolar spaces and interstitial tissues accompanied by hemorrhages The septal capillaries are frequently plugged by hyaline thrombi In fully developed lesions the interstitial and interalveolar spaces contain abundant fibrin and a great number of lymphocytes macrophages and desquamated alveolar epithelial cells The composition of the alveolar exudate slight infiltration of the alveolar septa and little change in large bronchioles and bronchi give the anatomic type of pneumonia in psittacosis a very characteristic pattern It is doubtless not absolutely specific since in etiologically proved cases the wide dilatation of the peribronchial and perivascular lymphatics packed with mononuclear cells is quite similar to lesions seen in interstitial pneumonias associated with other viral agents However *Binford and Hauser* were able to note definite differences in the microscopic lesions produced in the lungs by psittacosis viral agents and those of Q fever or other virus pneumonias According to Polayes and Lederer (1932) the edematous swollen hemorrhagic larynx epiglottis and trachea show microscopically a mononuclear exudate with areas of extravasated blood All cells in the alveolar exudate and the lymph sinuses of the hilar lymph nodes show active phagocytosis and intracytoplasmic elementary bodies

In the **liver**, which is slightly enlarged with parenchymatous degeneration the characteristic microscopic lesions are paracentral or centrolobular focal necroses A proliferation and accumulation of macrophages and hyaline thrombi in the sinuses and interstitial tissues precede the development of necrosis Kupffer cells contain the elementary bodies The usual changes in structure of the **spleen** are those of an acute tumor having relatively small follicles and engorged sinuses filled with phagocytic cells Cloudy swelling and hypertrophy of the muscle are the principal changes in the **heart** Varying degrees of degenerative changes involve the parenchyma of the **kidneys** Hemorrhages and capillary thrombi have been observed in the adrenals in infections caused by the highly toxic Louisiana virus Congestion and edema of the **brain and spinal cord** are not infrequent Sprunt and Berry (1936) found no evidence of changes in the neurons but proliferative and degenerative changes in the capillary endothelium and hemorrhages which they attribute

to toxic factors secondary to the presence of pneumonia On the other hand Polayes and Lederer (1932) demonstrated proliferation of neuroglia and changes in the neurons they could find no evidence of demyelinization as claimed by Peterson et al (1930) and others

CLINICAL ASPECTS

Clinically recognized psittacosis in man is a severe illness with a high mortality in the older age groups of both sexes Mild ambulatory cases and latent infections occur in fact persons exposed to the same infective agent may suffer from the disease in completely different degrees of severity The duration of the actual disease is usually 2 to 3 weeks Convalescence is nearly always protracted and tedious

SYMPTOMATOLOGY

From the many clinical descriptions published since 1879 (Hegler Adams Sturdee and Scott Hutchinson Rowlands and Simpson Peterson Spalding and Wildman Thomson and Hillier 1930 Grassi et al and Parros 1940 Garcia 1940 Lozzola et al Loizaga and Averbach) the strikingly uniform manifestations confused with influenza atypical pneumonia and typhoid fever repeat themselves with remarkable regularity A characteristic of the disease is the disparity between the extent and severity of findings discovered upon physical examination and the superficial appearance of well being which the patients exhibit only to be followed abruptly by a state of collapse

The incubation period, when determined with certainty varies from 7 to 14 days (average 10 days) after exposure 2 to 3 weeks may elapse between the acquisition of birds and onset of the first case In 3 cases in which single exposures occurred for a few hours the incubations were 7 8 and 9 days respectively An interval of 8 13 and 30 days respectively elapsed between the onset of illness and the discharge of three nurses from care of psittacosis patients When the disease is transmitted from one human case to another it may have an incubation time as short as 4 to 6 days (Hegler 1930 Sturdee and Scott 1930 Loizaga and Averbach 1945) An exceptionally long incubation of 82 days (Armstrong et al 1930) may possibly be explained as a relapse of latent infection provoked by another intercurrent infection

The onset may be sudden with chilly sensations fever anorexia sore throat general malaise and severe headache or the first symptoms may often be very vague and the beginning of the illness gradual and insidious **The fever** in many respects similar to that of typhoid fever is usually 100° to 102° F with a gradual rise of the stepladder variety During the second week in severe cases the temperature maintains itself at a high level with slight morning remissions even in fatal cases or may fall to normal about the seventh or eighth day in mild cases Termination by crisis is rare and during convalescence the temperature may be subnormal **The pulse** is apt to be slow in relation to temperature Nose bleed occurs in 25 per cent of the cases The

headache may be occipital nuchal or frontal it is intense intractable and not relieved by the usual analgesics

Except in mild cases **pulmonary involvement** manifest by its objective signs *is an essential* feature of human psittacosis A slight irritating dry cough during the first few days may persist or increase in intensity to painful paroxysms, cough despite extensive lung signs may be insignificant or absent throughout the illness The sputum is always scanty or entirely absent it is at first mucoid but later may become mucopurulent In rare instances it is tinged with blood usually when copious secondary infection is an accompaniment Abnormal signs about the lungs are often scanty The earliest demonstrable changes may be confined to an area of dullness on percussion at the bases of the lungs Crepitations may be heard as early as the fifth *day Usually the real* extent of pneumonitis is not evident until roentgenologic examination is made The wedge shaped appearance of the early pulmonary process is frequently of diagnostic significance as well as the scattered *patchy areas of consolidation over one or both lungs which give psittacosis* the picture of a migrating pneumonia Pleural reaction is generally slight or absent Physical signs begin to disappear by the beginning of the third week but x ray examinations disclose a slow but ultimately complete resolution Despite extensive involvement of the lungs the rate and depth of respirations are not increased except in fatal cases in which a rate as high as 60 has been reached

The relative slowness of the **pulse** is a characteristic feature throughout the course of the illness In nearly all fatal cases the pulse becomes rapid and weak cyanosis and low blood pressure may be marked, collapse at some time during the illness is common Thrombophlebitis has been known to occur and may cause relapses and death due to pulmonary thrombosis Insomnia restlessness followed by drowsiness disorientation apathy mental depression and even delirium may occur in *all except mild cases Photophobia* accompanies the headache

The **gastrointestinal tract** is involved in most cases Nausea and vomiting are common early *symptoms The tongue is furred Either* constipation or diarrhea may be present The spleen is palpable in very few cases Albuminuria of varying degrees is not infrequent and *transient glycosuria* has been reported Skin rashes or rose spots have been noted by Gastou (1892) Horder and Gow (1930)

The **blood picture** in psittacosis is not markedly altered The leucocyte count is usually normal or subnormal definite leucopenia is found in only 25 per cent of the patients Leucocytosis occurs late in the acute phase or in early convalescence No significant abnormalities are noted in the hemoglobin percentage or in the bleeding and coagulation times

Relapses particularly in cases inadequately treated with serum or penicillin are by no means uncommon With the aid of newer diagnostic procedures and in the course of epidemiologic surveys mild and inapparent infections are being recognized with increasing frequency *The symptomatology*

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sons has been used In general doses of from 50 to 200 c c have been administered intramuscularly or intravenously It is difficult to judge *objectively* the value of the treatment since neutralizing antibodies are rarely present in the sera and in animal experiments human convalescent serum exerted no curative effect In the early experiments by Rudd and Burnet (1941) and unpublished observations of Eddie and Meyer *there is no experimental proof that any of the sulfonamide compounds is of value on two strains of the psittacosis virus* More recently Meiklejohn et al (1946) have shown that sulfadiazine is effective against two classical strains which may in part explain the clinical cure reported by Hinshaw (1940) Significant and in harmony with the biology of the viral agent are the observations that mice which survived *the infection became carriers after therapy was discontinued*

In view of the *greater effectiveness of penicillin* on all the strains thus far tested there is no need to resort to sulfonamide therapy Heilman and Herrell (1944) Bedson and May (1945) Meiklejohn et al and Wiseman et al (1946) produced evidence that experimental psittacosis in the mouse responds to treatment *with penicillin* The workers at the Hooper Foundation (Meyer and Eddie 1947) treated experimentally infected mice and ricebirds Therapeutic results were convincing provided treatment was instituted early in the course of the infection and the antibiotic was used in large doses Ricebirds were apt to die from relapses 22 to 27 days after intensive treatment with 6 000 000 units over a period of 17 days had been discontinued *Successful* treatment of human psittacosis has been reported by Turgasen (1944) Flippen Gaydosh and Fittipoldi (1945) and by Meyer and Eddie (1947) Observations suggest that the antibiotic acts on the extracellular phase of the viral agent when it is not actually multiplying Whenever the immunity mechanism is sluggish or impaired by toxin action *penicillin treatment must be prolonged* until the antibodies of the host are capable of taking over the bacteriostatic and bacteriolytic effect of the antibiotic The dynamic action of penicillin on psittacosis specifies a high dose level (40 000 to 100 000 units every 4 hours) in rapid succession early in the course of the infection in order to reduce the number of viral elements and to permit the normal body *defense* mechanism to dispose of the few stragglers Adherence to these principles *will greatly reduce* the unduly high human case fatality rate from psittacosis and prevent the development of virus carriers

LABORATORY DIAGNOSIS

The laboratory diagnosis of psittacosis requires considerable time and the ultimate isolation of the specific virus in the sputum or blood is *from* the patient s standpoint largely an academic matter Therefore recourse is *made to the indirect method of diagnosis* which consists of the demonstration of specific antibodies

Isolation of the Virus During Acute and Convalescent Phase of Psittacosis and at Autopsy—During the acute and convalescent phase of suspected cases of psittacosis every effort should be made to isolate the virus by inoculation *of mice with specimens of citrated* human blood or sputum when they are ob

of mild cases has been described by Sturdee and Scott (1930) The patient is feverish with headache and general pains in the limbs and the attack may last for only a few days

DIFFERENTIAL DIAGNOSIS

Definite as is the clinical entity of psittacosis in man nevertheless certain diagnosis in any one case and in any one stage of such a case may offer great difficulty A typhoid like illness with pulmonary involvement and negative Widal test is very suggestive of psittacosis A clean cut separation of the patients from those who have pneumonitis due to other causes is quite difficult (Reiman 1947) Furthermore the response of the lung tissue to psittacosis infection resembles that described for other viruses Clinically roentgenologically and pathologically the psittacotic pneumonias resemble the severest forms of commonly occurring viral pneumonias A history of association with birds suggests a diagnosis of psittacosis but recently cases of influenza or so called atypical pneumonia with no definite history of avian exposure have been ultimately diagnosed as psittacosis Moreover recent facts definitely contradict the observation that a person to person type of spread prevails in influenza only

PROGNOSIS

The prognosis of psittacosis is difficult As long as the pulse remains below 100 the ultimate outcome is invariably good Until recently the *case fatality rate* of reported cases has been uniformly high (approximately 20 per cent) in the United States Germany and Argentina In the 167 cases reported by Armstrong it was 24 per cent in 301 other cases it was 17 per cent In a house epidemic due to parakeets observed by Meyer Eddie and Stevens (1935) all four victims died According to Fortner and Pfaffenberg the rate in Germany for 106 cases was 18 per cent in 1933 1934 then 20 per cent but it rose to 36 per cent in a group of 25 cases in 1937 1938 (Haagen and Mauer) The 186 cases described in the *Rev med Argentina* had a fatality rate of 39 or 20 per cent however in the outbreak described by Loizaga and Averbach the fatality in 28 cases was 13 or 46 per cent With the recognition of mild and ambulatory infections the case fatality rate in a series of 228 cases studied between 1940 and 1946 dropped to 21 or 9 3 per cent (Meyer and Eddie 1947) As a rule the age groups 40 to 60 are particularly liable to fatal infections With the introduction of penicillin as a therapeutic agent it is anticipated that the fatality rate will be further reduced

TREATMENT

Symptomatic treatment and careful nursing should be conducted along lines similar to recognized procedures used in pneumonia Isolation in a quiet environment is imperative in order to reduce the risk of person to person transmission Since 1930 the *serum of convalescent* and even of normal per

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tainable The diagnosis of human psittacosis is usually made in retrospect since not infrequently the virus is present in small quantities and repeated animal passage may be required for its demonstration (see Rivers and Berry 1935 Bedson 1936 Systematic inoculation of lung and splenic tissues from autopsies with lesions of pneumonitis has with increasing frequency led to the isolation of the psittacosis virus In a series of 228 cases of clinically and serologically proved psittacosis the nature of the infection was established in 52 or 22 per cent (Meyer and Eddie 1947)

Complement Fixation Test—Demonstration of complement fixing antibodies is being used with increasing success to demonstrate that a given acute illness is caused by a member of the psittacosis lymphogranuloma group Although at present it is impossible to differentiate sharply between human psittacosis and lymphogranuloma venereum serologic tests are frequently the only means of making a rapid diagnosis (see Meyer 1942 Smadel et al 1943)

The ubiquity of elementary body viral agents capable of inciting antibodies in man places restrictions on the diagnostic value of the complement fixation test In persons not previously exposed to viruses of the psittacosis lymphogranuloma group complement fixing antibodies may appear in the sera as early as within a week (fourth to eighth day) after the onset of symptoms If the titer rises within the next 4 or 5 days a tentative diagnosis of psittacosis may be rendered and specific treatment instituted Additional serum specimens should be examined and the rise in titer noted A serum with a titer of 1 16 or greater when obtained from a patient with clinical manifestations suggestive of psittacosis may be considered positive as a rule a fourfold or more increase in titer is observed during convalescence Precautions are necessary in the interpretation of the tests

Patients with a positive Wassermann reaction may react strongly with the psittacosis antigen when they are simultaneously infected in a latent stage with the virus of lymphogranuloma (Rake and Jones 1944) The sera of patients with acute infections may occasionally yield significantly high complement fixation titers which fade during convalescence in contrast to the psittacosis infections in which the titer rises during convalescence and usually persists for many months even years These fleeting reactions are probably anamnestic and may result from the reappearance of antibodies indicative of a previous unrecognized latent infection Individuals constantly exposed to psittacosis agents such as aviary owners pet shop employees pigeon breeders etc as a rule show complement fixing antibodies in their sera in titers varying from 1 8 to 1 32++++ (see Meyer 1942) Cold agglutination of erythrocytes and agglutinins for streptococcus MG do not appear in significant titer in psittacosis (Finland 1945)

PREVENTION

Prevention of psittacosis is difficult because the nature of the disease is recognized only when it appears in epidemic form Rigorous isolation should be applied to all severe cases during the febrile and acute clinical stages of the disease Patients with coughs should not be examined or treated without

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WESTERN TYPE OF EQUINE ENCEPHALOMYELITIS

Eklund and Blumstein (1938) reported 6 cases of encephalitis among farmers in Minnesota in 1937, all of whom had been in contact with horses sick with equine encephalomyelitis. Two of the men died after an illness of four to five days, and the third after an illness of weeks. It was found that the serum of 1 of the surviving 3 neutralized the Western strain of equine encephalomyelitis virus (in January, 1938). Howitt (1938), during the California outbreak, isolated a "Western" strain from the brain of a child, and in the next year from the blood of a man showing symptoms of encephalitis. Fothergill, Holden, and Wyckoff (1939) isolated the virus from the spinal fluid. Wheeler (1941) reported that 50 per cent of patients with encephalitis in Kansas showed antibodies for this "Western" type.

The Western variety of equine encephalomyelitis has been recognized as one of the most prevalent forms of encephalitis. In the summer of 1941 alone, 1,700 cases were recorded in Minnesota and North Dakota. Howitt (1942) examined 498 human sera from cases with diseases produced by neurotropic viruses and found that 213 (42.3 per cent) neutralized the Western virus. Leake (1941) reported on a large epidemic which occurred in North Dakota, recording 96 deaths from a total of 1,080 patients, an incidence of 167 per 100,000 and a mortality rate of 8.9 per cent. Wheeler (1941), Casals, Curnen, and Thomas (1943), and Lennette and Koprowsky (1943) reported laboratory infections and emphasized the high contagiosity.

LATIN AMERICAN STRAINS OF EQUINE ENCEPHALOMYELITIS

Rosenbusch (1935) isolated in Argentina a horse virus similar to the Western type. Tabusso (1935) and Schmidt (1936) found the same type in Peru and Chile, respectively. Kubes and Rios (1939) found in Venezuela a new encephalomyelitis virus that was reported again by Soriano Lleras and Figueroa (1942) from Colombia, and by Kubes (1943a) from Trinidad.

Shahan and Giltner (1945) reported that in 1944 an epizootic of equine encephalomyelitis occurred in Cuba; five strains submitted for examination were of the Eastern type. A vaccine was prepared from one of the Cuban strains. This protected equally well against the homologous strain, one of the other Cuban strains, and a representative Eastern virus from the United States.

Early in 1945, a sample of guinea pig brain, from infection with a supposed equine encephalomyelitis virus, was received from Ecuador. Guinea pigs immune to Eastern and Western virus succumbed to intracerebral inoculation with this virus. All guinea pigs immunized with Venezuelan type vaccine withstood intracerebral challenge with approximately 100 M.L.D. of the Ecuadorian virus, which was thus diagnosed as the Venezuelan type.

The vaccine prepared with the Venezuelan strain conferred complete protection against the homologous virus and the virus isolated in Trinidad (Kubes, 1943).

In 1913 and 1915 the Brazilian literature recorded clinical observations on equine encephalomyelitis. In March, 1937, in Tatuhuy, state of São Paulo, an epizootic was studied by Carneiro (1937). The virus isolated at that time seemed to be similar to the Argentina (Western) virus, but in further trials made by Carneiro and Cunha (1943) and Carneiro (1944) it was not possible to detect immunologic relationship between the Brazilian, the Argentinian, a strain of Western type from California, and the Venezuelan type viruses. The immunologic relationship to the Eastern type virus is much closer, though incomplete. To these authors it seemed that the Brazilian strain should be classified as a variety of the Eastern type.

According to Valdés et al. (1943), there was an epidemic of meningoencephalomyelitis in Córdoba, Argentina, during the autumn and summer of 1940 and 1941. Some scattered

CHAPTER 21

ENCEPHALITIS AND ALLIED DISEASES

Luis Vargas

EQUINE ENCEPHALOMYELITIS

The first published reference to equine encephalomyelitis is attributed to Large of the New York City Veterinary College, who in 1867 described the disease among horses on Long Island. The next paper was published by Williams (18[illegible]8) who described an outbreak in the Snake River Valley of Idaho. Buckley and MacCallum (1901) reported on an outbreak of equine encephalomyelitis in Maryland. Meyer, Haring and Howitt (1931) reported that in their investigation of a highly fatal outbreak among horses and mules in the San Joaquin Valley of California they isolated a filtrable virus responsible for the epizootic disease then prevalent. As the [illegible] was found to produce inflammation of both the brain and spinal cord they designated it [illegible] encephalomyelitis. This strain later was designated as the Western strain of equine encephalomyelitis. The first case appeared in July and continued to occur in large numbers until the advent of cool weather in October and November, when the disease disappeared. In the San Joaquin Valley outbreak in 1930 about one horse in ten was involved; from approximately 5[illegible] per cent of the cases terminated fatally.

EASTERN TYPE OF EQUINE ENCEPHALOMYELITIS

According to Randall (194[illegible]) in 1933 the disease appeared in horses along the Atlantic Seaboard (Giltner and Shahan, 1933) and Ten Broeck and Merrill (1933) reported isolation of an Eastern strain of equine encephalomyelitis virus which, though similar to the Western type, differed from it immunologically.

Epizootics of the Western variety among horses have been characterized by a high attack rate, a low fatality rate and a subacute form of the disease. Epizootics of the Eastern variety are characterized by a low attack rate, a high fatality rate and a more acute and fulminating type of disease. The areas of Eastern and Western equine encephalomyelitis are divided by the Appalachian range of mountains. In Alabama, which lies directly at the southern end of this mountain range, both forms of the malady are known to have occurred. In the spring of 1941 Randall and Eichhorn (1941) isolated the Eastern strain from a suspected horse from Brownsville, Texas. Téllez Girón and Valdez Ornelas (1941) identified the same strain in an outbreak in the state of Tamaulipas, Mexico.

Meyer (193[illegible]) suggested the possibility of human infection. He reported briefly 3 cases of encephalitis [illegible] in men closely associated with horses having equine encephalomyelitis. He was unable to isolate the virus from a fatal case or to demonstrate neutralization of the virus of equine encephalomyelitis by blood serum obtained during convalescence from a nonfatal case. He presented these cases with the suggestion that in the future the central nervous systems of patients who have died of typical human encephalitis be investigated for the presence of the virus of equine encephalomyelitis. Fothergill, Dingle, Farber and Connerly (1938) and Webster and Wright (193[illegible]) isolated in Massachusetts the Eastern type virus from human brains coincident with an epizootic in horses. It was the first time that equine encephalomyelitis had been demonstrated in infected species other than horses and mules.

The virus of Japanese encephalitis has been isolated from *Culex pipiens* var *pallens* and *Culex tritaeniorhynchus* in epidemic areas by both Russian and Japanese workers, and Culex, *Aedes togoi*, *Aedes albopictus*, and *Aedes japonicus* have been shown to be capable of transmitting the disease to mice or monkeys in the laboratory. Mitamura et al (1937, 1940) reported that mosquitoes bred in the laboratory from larvae or eggs collected in an epidemic area were occasionally infected. It has been reported that a virus of encephalomyelitis infection of mice somewhat similar to Theiler's virus is encountered in laboratory mouse colonies in the East, which, clinically, in animal susceptibility range, and even serologically, cannot be readily differentiated from Japanese B virus encephalitis. To prevent the establishment of this virus from accidental introduction we must control more species than Anopheles and *A aegypti* near air and seaports. The genus Culex and certain other genera can no longer be considered mere pests.

Mitamura et al (1940) reported the transmission of St Louis virus by *Culex pipiens* var *pallens*, *Culex tritaeniorhynchus* and *Armigeres obturans*. The Western type was transmitted by Culex.

Hammon and Reeves (1945) report that more detailed laboratory tests on inoculated chickens have shown that a very high dilution of St Louis virus, if inoculated subcutaneously into a chicken, gives rise regularly to a virus concentration in the blood to a titer higher than in the inoculum, for a period of 2 or 3 days, occasionally for as long as 4 days. No mammal thus far tested has proved to be as good a potential source of mosquito infection. However, despite this apparently satisfactory and well established concept of the epidemiology of this disease, mosquito fowl mosquito and occasionally a biologically aberrant infection mosquito to man or horse, the cycle is still incomplete. Chickens and other birds tested have shown no evidence of ability to serve as chronic or latent carriers of the virus. Hibernating *C tarsalis* and *C pipiens* collected during the winter in Washington and California have not been found infected so far, although 5,429 have been tested. These results do not support the early hypothesis of winter "carryover," presented by Hammon et al (1941, 1942) based on the fact that many Culex hibernate as adults. In addition, they tested the eggs and progeny of infected *C tarsalis* and *C pipiens* and found no evidence of transovarian passage of the virus. Therefore, the true reservoir or the whereabouts of the virus during the winter and during the seasons when there is no apparent infection is unknown.

Hammon and Reeves (1945) state that one strain has just been isolated from *Aedes dorsalis* (Meigen) caught in Kern County, California. This is the first isolation of St Louis virus from any source in California, although serologic evidence of its presence had been repeatedly obtained. It is also the first isolation of St Louis virus from an Aedes mosquito.

In the West, most of the cases have occurred among adult male farm workers in contrast to the Eastern type infection which has had the highest incidence in children. In 28 cases studied in the Yakima Valley, Washington, by Hammon et al (1945), the mean age was 36, as compared with 46 for 1940 and 25 for 1941. They recorded 4 cases in children less than 1 year old, males greatly predominating only in the adult and teen age working group. By using five New Jersey type light traps, they showed that the activity of *C tarsalis* correlated well with the epidemic curve.

Hammon and Reeves (1942, 1943, 1943a) have demonstrated that *C tarsalis* is an efficient vector of both Western equine and St Louis viruses. It feeds predominantly on fowl and occasionally on mammals. It becomes readily infected by feeding on fowls at a time when virus is present in the blood, and mosquitoes infected become, in turn, infective by their bite after a suitable extrinsic incubation time at proper temperatures. It thus appears that this species is an important vector of both Western equine and St Louis viruses.

Hammon and Reeves (1945) found *C pipiens* infected with St Louis and Western equine viruses. This species is also used in the laboratory as a vector of St Louis virus and thus can be considered a natural vector. However, in all laboratory tests, this species has lost every detectable trace of Western equine virus in 24 hours. It would appear that the recovery of Western equine virus from a mosquito of this species in nature is an indication that the

cases had previously been observed, but this was the first epidemic of encephalitis to be recognized in Argentina The author observed 80 cases in the University Hospital, with a higher incidence in children Of 67 seriously ill patients, 40 per cent died, and 16 per cent presented serious aftereffects such as hydrocephalus, epilepsy, and mental disturbances Of the entire group, only 44 per cent recovered without sequelae Neutralization tests with convalescent sera were negative with the Japanese B and St Louis, as well as Eastern and Western equine encephalomyelitis viruses.

The infection was transmitted to white mice by inoculation of an emulsion of brain material, it was possible, too, to convey the infection from mice to mice The epidemic coincided with an epizootic in horses and was followed by one in birds

In Cordoba Argentina, cases of infantile encephalitis have been confirmed several times since late in 1940 Valdés et al (1943) observed cases in children born of apparently healthy mothers These authors described 8 cases at ages ranging from 5 days to 9 months, all were studied clinically and pathologically and presented the first signs without any exception a few hours or days after birth

Soriano Lleras (1943) pointed out that Ordonez in 1943 reported that in Bogotá and Tenjo he had observed 7 human cases of encephalomyelitis He added that the disease was described for the first time in Colombia by Franco in 1923 Guerrero, in 1927, collected 6 more cases, one in La Dorada and five in Bogotá Ordonez in 1940 observed the disease in Bogotá Bucaramanga La Dorada and Tenjo, but the etiologic agent was not clear It is believed that there was a severe outbreak in that year Early in 1941, in La Sabana, and especially in Bogotá equine encephalomyelitis appeared in epidemic form, Soriano Lleras (1943) established that the agent was the Venezuela type virus The rarity of human cases contrasts with the frequency with which equine encephalomyelitis appears this having been studied by Tavares in Tolima more than twenty years ago later, epizootic outbreaks occurred in El Cauca, Atlantico, Valle, Tolima Bolivar, Huila Magdalena, La Guajira, Arauca, Cundinamarca, and Antioquia

TRANSMISSION

It has been observed that the disease appears in early summer, reaching its peak late in August or September and disappearing with the coming of killing frosts Infection follows natural water courses and irrigation systems, Its greatest prevalence is in rural areas among horses kept in the pastures at night Meyer et al (1931) had expressed the belief that the virus is transmitted by an insect vector

Kelser (1933) proved that the mosquito *Aedes aegypti* is capable of transmitting the virus of equine encephalomyelitis from guinea pig to guinea pig and from guinea pig to horses It was further shown that the transmission was not mechanical but occurred after multiplication of the virus within the mosquito and that once infected the insect was capable of transmitting the disease for most, if not all of its ordinary life Simmons Reynolds and Cornell (1934) proved transmission of the disease by *Aedes albopictus* Merrill, Lacaillade, and Ten Broeck (1934) succeeded in transmitting both Eastern and Western strains through *Aedes sollicitans*, the New Jersey salt marsh mosquito, and also *Aedes cantator* Madsen and Knowlton (1935) added *Aedes nigromaculis* and *Aedes dorsalis* to the list of transmitters, and Ten Broeck and Merrill (1935) and Kelser (1937) added *Aedes vexans*, Kelser (1938) added *Aedes taeniorhynchus*, Davis (1940) added *Aedes triseriatus* to this group of experimentally infected mosquitoes Hammon et al (1941) reported that *Culex tarsalis* was found to be harboring the virus in nature They found that the same species of mosquito harbors the virus of St Louis encephalitis Hammon and Reeves (1943) demonstrated transmission by *Aedes lateralis* (Meigen) Syverton and Berry (1936) showed that the Rocky Mountain spotted fever tick, *Dermacentor andersoni*, is capable of transmitting the disease experimentally from guinea pigs to ground squirrels and further suggested that the gopher, *Citellus richardsoni*, may be the natural host of the virus because of its susceptibility

first isolated appeared to be of low virulence but the virulence was built up rapidly by serial passage. The virus also killed consistently following intranasal instillation and foot pad inoculation.

IDENTIFICATION AND PROPERTIES

The virus of equine encephalomyelitis is estimated to be from 20 to 30 mμ in size. It may be preserved in 50 per cent glycerin under refrigerated conditions for some time. It apparently loses its virulence quite readily in a dried condition. It is easily destroyed by heat and by chemical preparations commonly used as disinfectants.

Calla (1944, 1945) investigated the in vitro effect of different drugs on the Venezuelan equine encephalomyelitis virus. No antibiotic known to date (1949) is effective.

SYMPTOMATOLOGY

Eklund (1942) and Leemster (1938) described the disease in human beings as follows: The clinical picture in human encephalitis of the Western type closely resembles the St. Louis disease. There is usually an abrupt onset with severe headache and high fever, together with chills, chilly sensations, nausea or vomiting, pain in the neck, the back, the abdomen, or in the extremities. In young children the onset is sudden, with high fever and convulsions. A day or two after the onset drowsiness appears, the temperature continues to be elevated. The patient becomes mentally retarded and when not disturbed drops off to sleep. Shortly thereafter tremors about the mouth and hands may appear. Delirium and disorientation take place in some cases; in others drowsiness progresses to coma. Rigidity of the neck muscles is the most frequent finding, but lack of abdominal reflexes and tremors of the lips, tongue and hands are common. Less frequent are positive Kernig and Babinski signs, abnormal tendon reflexes, difficulty in speech and swallowing are rather uncommon except in children. Mental retardation and paralysis sometimes occur. The temperature is high for about five days, then it drops rapidly. About two days after the temperature declines the symptoms improve and in ten to fourteen days the patient is well on the road to recovery.

In fatal cases the fever continues high, drowsiness progresses to coma, and death usually follows in 5 to 7 days. The mortality from the Western type appears to be about 10 per cent, although 7 to 20 per cent have been reported.

In the Eastern infection, onset is more abrupt, pointing to an early and severe invasion of and injury to the central nervous system; high fever, vomiting, and appearance of drowsiness or coma all becoming manifest in 24 to 48 hours. The cerebrospinal fluid is under increased pressure, of hazy to ground glass appearance, with cell counts varying from 200 to 2,000 per cubic millimeter, from 60 to 90 per cent of the cells are polymorphonuclear leucocytes. There is a high fatality rate (75 per cent), a predilection for children and marked sequelae in the survivor, such as paralysis and mental changes.

According to Adamson and Dubo (1942), a patient affected by equine encephalitis Western type has the aspect of and acts like a person alcoholically

specimen had recently engorged on an infected reservoir and that the virus probably would have disappeared within a few more hours.

Culiseta inornata is capable of acting as a vector in the laboratory and if present in large numbers might serve as a vector of importance. *Anopheles freeborni* has been demonstrated to lose all detectable virus within 4 hours.

The Western type of equine encephalomyelitis virus was isolated by Sulkin (1945) from chicken mites *Dermanyssus gallinae* (de Geer) in nature during an outbreak in which there were at least 3 cases of infection in man. Smith, Blattner and Heys (194) reported the isolation of the St. Louis virus on three different occasions from *D. gallinae* and demonstrated the infection in the progeny.

It is believed by Gallyard (1944) that in Trinidad the principal vector may be *Taeniorhynchus titillans* but other species cannot be excluded. The virus has been isolated from mosquitoes captured in the field and the vaccine elaborated with the Venezuelan virus has fully protected experimental animals against it. A fatal human case is reported in a sailor about 40 kilometers distant from the animal outbreak and is considered as the first human case of equine encephalomyelitis virus Venezuelan type. *T. titillans* is a common mosquito ranging from the southeastern states of the United States to South America. This author was able to demonstrate for the first time a mosquito to infect on from a large mammal with any of the equine viruses. This is therefore another arthropod-borne virus encephalitis affecting man with large mammals including horses and man among the hosts from which mosquitoes may become infected. Similar in this respect is the Japanese B virus.

In some experiments *Stomoxys calcitrans*, *Tabanus punctifer* and *Haematobia serrata* were not proved to be capable of being vectors of equine encephalomyelitis.

Remlinger and Bailly (1936, 1936a) reported a large number of birds to be susceptible to the Argentine virus. These included the greyleg goose (*Anser cinereus*), the black (*Circus rufus*), the European blackbird (*Turdus merula*), the tawny vulture (*Vultur fulvus*), the white stork (*Ciconia ciconia*) and the mallard duck (*Anas boschas*). The Argentine virus is immunologically identical with the Western virus.

Nevertheless the reservoir of the encephalomyelitis virus is unknown. The horse does not seem to be a suitable reservoir according to Randall (194?) since the virus can be isolated from its blood stream only during the early stages of the disease and a chronic carrier state has not been established. Pheasants, pigeons and prairie chickens have been found infected under normal conditions. Hammon et al. (1941), working in the Yakima Valley, found the blood serum of many mammals and birds from the region to show neutralizing antibodies to the virus. The avian species included the chicken, goose, dove, pigeon, turkey, flicker, killdeer, pheasant and quail; the mammals included the cow, dog, goat, horse, pig, sheep, field mouse and weasel. This indicates the wide host range of the virus. As mosquitoes readily feed on mammals and birds this further stresses the importance as vectors of the disease.

Inoculation into a wide variety of vertebrates by dermal routes has not afforded any results suggesting a true reservoir state but Blattner and Heys (1944) found that *Dermacentor variabilis* (Say) is capable of transmitting the infection and that transovarian infection occurs, thus suggesting a potential reservoir. Hammon and Reeves (1945) note however that no naturally infected ticks have been found and there is little to suggest that the dog might serve as a link to infect ticks. Moreover *D. variabilis* is unlikely at any stage in its development to infest fowl. These authors found a heavy chicken tick infection of *Argas persicus* (Oken) in the San Joaquin Valley. However none was found infected among 9,9?8 tested during 1943 and 1944 but in the laboratory experimental infection has persisted at least ...

Syverton and Berry (1936) were able to infect *D. andersoni* and they demonstrated transovarian infection.

Kitselman and Grundmann (1940) isolated the virus fatal to guinea pigs from *Triatoma sanguisuga* Leconte collected from a pasture near Carrison, Kansas. The virus when

from the brain at autopsy. It has rarely been isolated from the blood or spinal fluid. Usually the diagnosis is made by the neutralization test in which a series of tenfold dilutions of the virus are made. Virus suspensions diluted 1:1 000, 1:10 000 and 1:100 000 are mixed with equal amounts of the patient's serum, and groups of mice are inoculated intracerebrally. If the patient has had the disease, the mice will be protected; serum may have protective power as early as one week after onset of the disease. The time when the serum has its maximum protective power is not known, but when taken at the end of the second or third week will probably in most cases show protection. Protective antibodies have been demonstrated in the sera of patients two years after recovery from the disease, and it is possible that they may persist longer. Sera of patients with no history of encephalitis seldom show protection, so that a positive neutralization test, together with the clinical findings of encephalitis, justifies a diagnosis of encephalitis of the equine type. It is preferable, if possible, to secure blood serum early and demonstrate that antibodies are not present early in the disease but are developed during the illness or convalescence.

As Shahan and Giltner (1945) state, infection by equine encephalomyelitis virus is almost invariably followed, in the event of recovery, by the formation of virus-neutralizing antibodies in the blood serum. In some few cases these may endure for a comparatively short time but they usually persist for months. The antibodies develop after inapparent or occult infections and after vaccinations with formalin-inactivated virus such as is utilized in the present-day chicken embryo vaccine.

Noran and Baker (1945) state that the lesions in Western equine encephalitis may be progressive, resulting in a chronic form of this disease, especially in infants and children. In one case they found that cysts had replaced both frontal lobes and were separated from one another by glial tissue. The rest of the brain represented widespread parenchymal changes consisting of diffuse and focal areas of demyelinization. The vascular involvement varied from collars of perivascular infiltrations to the narrowing and occlusion of the vessels by an endothelial proliferation. Vascular calcification was prominent. Apparently the vascular alterations indicate that the parenchymatous lesions are secondary to cerebral ischemia. The outstanding pathologic changes in the blood vessels suggest a vascular spread of the equine virus.

Kubes (1943) systematically studied the immunologic relations between the Colombian and Venezuelan viruses. The results obtained suggest the immunologic identity of both viruses. Nevertheless the antigenic potency of the vaccine elaborated with the Venezuelan virus is higher than with the other.

Havens et al. (1943) found a definite cross reaction in the complement fixation test between Eastern equine encephalomyelitis and Western encephalomyelitis viruses. On the other hand the conclusions reached by Casals (1945) were that by complement fixation test with guinea pig hyper

intoxicated in the first degree showing a red face sweat, tumefaction with mask expression and redness of the eyes and nose Speech is difficult, there are tremors of the tongue lips and hands Notwithstanding the intense cephalalgia somnolence and mental confusion the patient seems to be only slightly worried about his condition and probably after recovery will not recall any details of his illness In addition the patient shows absence of abdominal reflexes but the Babinski sign is positive there is nystagmus and the cerebrospinal fluid shows monocytes

The most convincing proof of the disease is a positive complement fixation reaction* or the neutralization test In localities in which equine encephalomyelitis has been observed an unknown proportion of the population perhaps may show positive blood reactions The serum may be negative during the first weeks and even later The test must be repeated in all suspicious cases

Clinically it is very difficult to differentiate the disease from poliomyelitis cases with slight encephalitis may resemble serious poliomyelitis cases In this latter perhaps one may observe cephalalgia somnolence sweating mental disturbances and abnormal reflexes characteristic of encephalitis Rigidity of the neck muscles and paralysis indicate poliomyelitis nystagmus tremors and monocytes in the cerebrospinal fluid all point to encephalitis The acute symptoms of poliomyelitis disappear within 4 to 5 days while those of encephalitis perhaps may last one week

The pathology of the disease in man is reported as similar to that described for animals. It is stated that in man the general type of pathology in lethargic encephalitis St Louis encephalitis and encephalomyelitis is practically the same the differences consisting chiefly in the degree and extent of involvement

Randall (1942) sounds a note of caution about brain material from fatal suspected cases submitted to laboratories for virus isolation shortly after death certain chemical changes take place with formation of lactic acid, that readily destroy the virus Therefore in suspected cases that end in death remove the brain promptly and place selected portions of it in sterile 50 per cent buffered glycerin The virus will remain viable for many days The brain material in a dilution of 1 100 should be injected intracerebrally into three groups of guinea pigs One group should be previously immunized against the Western type the second group against the Eastern type and the third group not immunized If equine encephalomyelitis virus is present all of the guinea pigs except those immunized against the specific type should die in 3 to 5 days In a typical case in man a diagnosis of encephalitis should not be difficult but it is impossible to state whether it is the St Louis or equine type It is often difficult to differentiate this disease from abortive poliomyelitis or tuberculous meningitis and when there are no neurologic findings from the common infectious diseases such as undulant fever An etiologic diagnosis can often be made The virus itself is most often isolated

*Editor's note (O F) Lederle Laboratories Inc and the Markham Laboratories, Chicago Ill produce reliable antigens for such tests

vessels become compressed or even obliterated The usual infiltrative elements are lymphocytes, plasma cells are rare and appear late in the infection other cells are the same as in the pia—polyblasts fibroblasts and rod cells They are all confined to the adventitial spaces of Virchow Robin In some cases the infiltrations are so dense that they overflow these spaces and invade the surrounding parenchyma The perivascular infiltrations are especially prominent in the substantia nigra around the Sylvian aqueduct, and in the optic thalamus Hemorrhage and softening are as a rule absent and polymorpho nuclear cells may be present in very acute or peracute cases Small scattered hemorrhagic foci occasionally may be seen but they are not associated with reactive glial phenomena and thus may be considered agonal

Poliomyelitis may resemble epidemic encephalitis The main differential feature however as pointed out by Hassin (1933) is in the parenchymatous changes which are present in the anterior horn cells in poliomyelitis Here within a few days or even hours the ganglion cells may become destroyed as evidenced clinically by sudden paralysis and early degenerative muscular atrophy In epidemic encephalitis the majority of the ganglion cells are un affected or exhibit only a slight cloudy swelling mild chromatolysis and occa sional neurophagia Mild as the inflammatory phenomena in the spinal cord are their presence in encephalitis justifies the designation of the latter as a disseminated encephalomyelitis

Koprowsky and Lennette (1944) found that the pathogenesis of the infec tion produced by the Venezuelan equine encephalomyelitis virus in chick embryos is similar to that of the Eastern and Western viruses There was no change in the virulence of the virus for mice as a result of membrane passages

One might expect that the clinical and histologic pictures of lethargic or any other forms of encephalitis would be affected by the duration of the disease the age of the patient the virulence of the infection and other factors Though a number of clinical varieties of epidemic encephalitis have been recog nized—hyperkinetic delirious tabetiform and other types—there is no mani fest pathologic difference

Hassin (1933) says that the specific feature of typhus encephalitis is an abundance of nodules and their widespread dissemination which spares no part of the nervous system The same may be said of the ganglion cell changes Ganglion cell changes occur throughout the brain and may be either mild as in encephalitis or very severe as in poliomyelitis

The nodules so much in evidence in typhus encephalitis are also very prominent in encephalitis which occurs in malignant endocarditis

Trichinosis encephalitis is a rather rare form of meningoencephalitis It shows a combination of mesodermal and degenerative phenomena Both are due to invasion by Trichinella larvae which can be demonstrated in the tissues of the brain or within the meninges

In rabies the central nervous system is in a state of inflammation a di seminated encephalomyelitis with the presence of Negri bodies The inflam matory foci are the same as in lethargic encephalitis

immune sera (1) Venezuclin equine encephalomyelitis virus is not related to either the Eastern or Western viruses, (2) two strains of the Western type differ in their capacity to develop the complement fixing antibody (3) the relationship between the Eastern and the Western types is doubtful Cross reactions rarely occur in 1:2 and 1:4 dilutions more often they arise in the same dilutions as nonspecific partial reactions since in that zone other antigens as well are reactive with the same sera

Casals (1945) reports that avirulent lyophilized antigens that ritiin their properties specificity antigenicity and lack of anticomplementary power for at least two years can be prepared with the Western type virus

At present the antigens of the Western type Eastern type lymphocytic choriomeningitis and St Louis viruses should be used as a routine practice* If the serum is anticomplementary or if a nonspecific reaction occurs the test should be repeated with serum inactivated at 56° C for twenty minutes If this procedure does not eliminate the nonspecific reaction the serum must be classified as unfit for the test

Guinea pigs are highly susceptible to Venezuelan Eastern and Western equine encephalomyelitis viruses From these animals hyperimmune sera can be obtained

ST LOUIS ENCEPHALITIS AND LYMPHOCYTIC CHORIOMENINGITIS

St Louis virus is pathogenic for mice and hamsters these two species are used for the production of hyperimmune serum for the St Louis and lymphocytic choriomeningitis viruses Casals (1945) has prepared hyperimmune sera which following inactivation at 56° C for 20 minutes had titers of 1:64 to 1:128 The serum is heated at this temperature following dilution *in order to prevent coagulation Sometimes a partial nonspecific fixation* of the complement occurs with the dilutions 1:2 and 1:4

Lymphocytic choriomeningitis hyperimmune sera have been obtained in mice only

PATHOLOGY

Encephalitis is the term commonly used for nonpurulent inflammation of the brain Only those clinical cases with virus etiology will be discussed According to Hassin (1933) in epidemic or lethargic encephalitis the ecto-dermal and mesodermal tissues of the brain are involved including the meninges pia arachnoid The meshes of the pia may be greatly distended and *may contain hematogenous elements mainly lymphocytes and plasma cells* Quite numerous around the congested and hyperemic blood vessels they are often mixed with fibroblasts polyblasts macrophages and rod cells The in-filtrating cells are present throughout the pia that is around every part of the brain especially around the cerebellum

Frequently the subjacent cortex is also infiltrated but *in general the* vascular changes here are milder than in the pia They are more marked in the subcortical areas mainly around the smaller veins Here the vascular infiltrations for instance may be so marked that the lumina of the blood

*Editor's note (O F) Obtainable from Lederle Laboratories Inc. and from Markham Laboratories

ck activity It has been estimated to be 15 to 20 mμ in size The virus is uickly destroyed at room temperature but may be preserved for considerable me at low temperatures It can be easily preserved in 50 per cent glycerin t 4° C

According to Merchant (1942) this disease may be easily transmitted y various means under experimental conditions to sheep and less regularly, o cattle goats and swine The virus has also been transmitted to monkeys ice and field voles Under experimental conditions the incubation period ap ears to vary from 5 to 9 days after intracranial infection Cases of human fection have been recorded as mild and of short duration followed by omplete recovery Sheep exposed to this disease under natural conditions sually show clinical symptoms in from 6 to 18 days The onset of the disease characterized by a high temperature and symptoms of a central nervous sturbance Progressive incoordination tremors clonic muscular spasms nd paresis are often observed Recovery often occurs without the develop ent of nervous symptoms Permanent irregularities in locomotion may ollow the manifestation of severe nervous symptoms Animals which have covered from this disease developed complete immunity

The Russian spring summer encephalitis differs from the remainder of is group principally in respect to paralytic manifestations Shoulder girdle aralysis or paresis is reported to occur quite frequently Virus has been olated from the blood the cerebrospinal fluid and the urine of infected per ns Case fatality rates average about 30 per cent The Russians have effec vely used a formalinized tissue vaccine to protect man in the areas involved

The name Japanese B encephalitis has been used to distinguish from the on Economo type which the Japanese called type A an epidemiologically nd clinically distinct type of epidemic encephalitis Hammon and Reeves 945) stated that they have demonstrated the ability of six species (three nera) of California mosquitoes to transmit the Japanese B virus to animals nd have demonstrated its presence in the blood of inoculated chickens The apanese and Russians themselves have reported transmission by only five ecies (two genera) This disease did not attract much attention until the eat epidemic of 1924 which involved over 6 000 persons with 3 797 reported aths Since then annual epidemics have been recorded sometimes from umerous regions Between 1924 and 1937 from Japan alone 21 355 cases ith 12 159 deaths were reported Case fatality rates have ranged from to 75 per cent Epidemics or sporadic cases have also been reported om Formosa the Southern Ryukyu Islands eastern China and the eastern S S R Smithburn and Jacobs (1942) reported as a result of serologic tests at ' the St Louis and Japanese B' viruses have been active over broad panses of territory in Central Africa Sabin (1943) reported a number positive serologic tests for Japanese B virus in the Cincinnati area

Smorodintseff et al (1940) had already shown that the Russian spring mmer encephalitis is different from the autumn encephalitis which is

CULTIVATION, TREATMENT, AND IMMUNOLOGY

Carneiro (1944) tested duck and goose eggs as to their suitability for virus culture The results were identical with those obtained with chick embryo

Intraperitoneal neutralization tests with the Venezuelan equine encephalomyelitis virus were found by Lennette and Koprowsky (1944) to be feasible in mice as old as 200 days Inoculations of serum virus mixtures subcutaneously into 3 day old mice, or intraperitoneally into 8 day old mice provided a highly sensitive means for detecting antibodies to the St Louis encephalitis virus. Tests in mice 14 or more days of age were less sensitive or not feasible With the viruses of Eastern and Western equine encephalomyelitis Japanese B encephalitis and West Nile disease, a highly sensitive test was afforded by the use of mice up to 14 days of age Tests in 21 day old mice were less sensitive or inadvisable because of lack of uniformity in the results Present evidence suggests that subcutaneous inoculation of test mixtures into 3 day old mice may constitute a more sensitive quantitative test than does intraperitoneal inoculation into older, but still highly susceptible, mice Where adequate susceptibility to extraneural (subcutaneous or intraperitoneal) infection exists this route of inoculation of serum virus mixtures is much more sensitive for the demonstration of neutralizing antibodies than the intracerebral route

Treatment

Supportive treatment mainly large volumes of physiologic salt solution fortified with glucose and given intravenously is indicated to overcome dehydration Medicinal treatment is largely symptomatic and should be conservative Good nursing is essential It is reported that lumbar puncture gives marked relief of headache

Immunization is very effective in animals Due to the number of deaths which have occurred among personnel working with these viruses, it is now general practice to vaccinate at least once yearly all laboratory workers employed in the manufacture of encephalomyelitis vaccine

Davison (1941) and Gold and Hampil (1942) have tried serotherapy in human beings but the results are inconclusive

Stramonium and scopolamine are recommended for insomnia and for muscular rigidity and spasm They act as cerebral sedatives and hypnotics

OTHER VIRUS DISEASES

Russian spring summer encephalitis occurs annually in forest regions of the eastern U S S R and to a lesser degree in European Russia It occurs only during the spring and early summer coinciding with the activity of ticks The virus has been isolated from man rodents, and ticks Casals and Webster (1943 1944) have shown it to be very similar to or identical with the virus of louping ill of sheep in Scotland also known to be tick borne Silber and Shubladze (1945) have reported that louping ill is the tick borne encephalitis of western U S S R but that a different virus is responsible for tick borne encephalitis in the Far Eastern area The tick is not only the vector but also the reservoir since transovarian passage of the virus normally occurs

Louping ill is transmitted by the sheep tick Distribution is limited to tick infested areas and its seasonal occurrence in April May, and early June and again in September bears a close relationship to the months of greatest

TABLE XIV—THE "ENCEPHALITIS" GROUP OF VIRUSES AND VIRAL DISEASES
(According to Felsenfeld)

VIRUS	MORTALITY AND UNUSUAL CLINICAL PICTURE (IF ANY)	VECTOR TO MAN	ANIMAL RESERVOIR	VECTOR TO ANIMALS	VIRUS ISOLATED FROM BLOOD AND C S F	EXPERIMENTAL ANIMAL TO BE USED	NEUTRALIZED BY SERUM AGAINST	NEUTRALIZES VIRUS	REMARKS
St Louis	Small	Mosquitoes	Fowl, horses	Ticks, mites	Rare	(Young) Mouse I C, rabbit I C, and guinea pigs I P not sensitive	Japanese B	West Nile	Neutralizing antibodies in serum appear late
Japanese B	High	Mosquitoes, ticks	Dogs, horses, goats, cattle, rabbits	As man, also helminths	Often	As St Louis	0	St Louis West Nile	As above
Eastern equine	High	Mosquitoes (ticks mites)	Horses, mules, donkeys, pigs, rabbits fowl	As man	Rare	Mouse I C, rabbits and guinea pigs I C sensitive	Brazilian virus related		
Western equine	Low	As Eastern					Argentinian virus related		
Venezuelan	High	As Eastern	Horses, mules donkeys	As man	Yes	As Eastern equine	Similar to Eastern equine		Rare in human beings
Far Eastern (Russian spring summer)	Medium	Mosquitoes, ticks	Horses, wild rodents, birds	As man	Rare	Mouse I C	Related to louping ill and West Nile		
Louping ill	None	Ticks	Sheep	Ticks	Yes	Mouse I C	Related to Far Eastern virus		Rare in human beings
Lymphocytic choriomeningitis	Very small	Mosquitoes, bedbugs helminths	Mice	As man	Often	Mouse I C, guinea pigs I C, rabbits not sensitive	Related to Humphrey's virus		Complement fixing antibodies appear first
Australian X disease	High	?	Monkeys	?	?	Monkey	Probably related to Japanese B		Virus was lost

identical with the Japanese B type Sabin (1943) reported the elaboration of a vaccine for experimental use in man

According to Grieg (1933) the virus of louping ill of sheep is transmitted in nature by certain ticks (*Ixodes ricinus*) Alexander and Neitz (1933 1935) transmitted the disease from infected to normal sheep by the nymphs of other ticks (*Rhipicephalus appendiculatus*) infected as larvae and by adults infected as nymphs This worker was unable however to demonstrate virus in eggs or larvae obtained from infected females The virulence of the infection appeared to be increased by passage through the tick hosts Smithburn et al (1940) isolated a virus which they have called the West Nile virus,' by the intracerebral inoculation of mice with serum from a mildly febrile woman in Uganda Africa It produces encephalitis in the mouse the monkey and the hamster Philip and Smadel (1943) have transmitted the virus in the laboratory by the bite of *A albopictus* mosquitoes The virus is related immunologically to the St Louis-Japanese B group Smithburn and Jacobs (1942) believe that the antibodies are specific for this virus in man

Bugher et al (1944) have isolated two unidentified viruses by the intracerebral inoculation of mice from mosquitoes caught in Colombia They called the viruses Sabethine I and Anopheles I from the genus of mosquitoes from which they were isolated

Hammon and Reeves (1945) in the summer of 1943 isolated from *A dorsalis* mosquitoes caught in Kern County California an unidentified virus (BFS 91) which produces encephalitis in mice cotton rats and hamsters and which can be cultivated by various methods in the chick embryo Sera from a number of encephalitis patients and from domestic and wild animals from the area in which it was found have neutralized it in protection tests In 1944 from the same area and from the same species of mosquitoes another virus (BFS 283) was isolated which also has proved to be difficult to identify and in all probability is identical to BFS 91

Evidence is therefore accumulating that there are a large number of arthropod borne neurotropic viruses of man and other animals and that they are of world wide distribution and of no small importance

The term acute lymphocytic choriomeningitis was suggested by Armstrong and Lillie (1934) This condition was formerly referred to as acute serous meningitis idiopathic meningitis acute benign lymphocytic meningitis meningitic form of encephalitis and acute aseptic meningitis

Armstrong and Lillie (1934) recovered an undescribed filtrable virus from a monkey to monkey transfer of infectious material from the brain of a patient who had died of encephalitis during the St Louis epidemic of 1933 Inasmuch as this virus is immunologically distinct from the encephalitis virus, producing in experimental animals an infiltration of round cells in the meninges and choroid plexus they designated it the virus of experimental lymphocytic choriomeningitis Scott and Rivers (1936) described a method of obtaining the virus from the cerebrospinal fluid and demonstrated that their virus likewise produced a characteristic histologic pattern in animals and was serologically

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(According to Felsenfeld)

VIRUS	MORTALITY AND UNUSUAL CLINICAL PICTURE (IF ANY)	VECTOR TO MAN	ANIMAL RESERVOIR	VECTOR TO ANIMALS	VIRUS ISOLATED FROM BLOOD AND C.S.F.	EXPERIMENTAL ANIMAL TO BE USED	NEUTRALIZED BY SERUM AGAINST	NEUTRALIZES VIRUS	REMARKS
St. Louis	Small	Mosquitoes	Fowl, horses	Ticks, mites	Rare	(Young) Mouse I.C., rabbit I.C., and guinea pigs I.P. not sensitive	Japanese B	West Nile	Neutralizing antibodies in serum appear late
Japanese B	High	Mosquitoes, ticks	Dogs, horses, goats, cattle, rabbits	As man, also helminths	Often	As St. Louis	0	St. Louis, West Nile	As above
Eastern equine	High	Mosquitoes (ticks, mites)	Horses, mules, donkeys, pigs, rabbits, fowl	As man	Rare	Mouse I.C., rabbits and guinea pigs I.C. sensitive	Brazilian virus related		
Western equine	Low	As Eastern					Argentinian virus related		
Venezuelan	High	As Eastern	Horses, mules, donkeys	As man	Yes	As Eastern equine	Similar to Eastern equine		Rare in human beings
Far Eastern (Russian spring summer)	Medium	*Mosquitoes*, ticks	*Horses*, wild rodents, birds	*As man*	Rare	Mouse I.C.	Related to louping ill and West Nile		
Louping ill	None	Ticks	Sheep	Ticks	Yes	Mouse I.C.	Related to Far Eastern virus		Rare in human beings
Lymphocytic choriomeningitis	Very small	*Mosquitoes*, bedbugs, helminths	Mice	As man	Often	Mouse I.C., guinea pigs I.C., rabbits not sensitive	Related to Humphrey's virus		Complement fixing antibodies appear first
Australian X disease	High	?	Monkeys	?	?	Monkey	Probably related to Japanese B		Virus was lost

Virus B	High Ascending myelitis	?	Monkeys	?	Yes	Monkey I C and I O	Related to herpes simplex and may be identical with W virus		Inclusion bodies, only laboratory infection in man
Swineherd s disease	Low Similar to dengue	?	Swine	?	During first phase	Monkey I C	0		Some claim that disease caused by Leptospira
Bwamba fever	None Similar to dengue	Mosquitoes	?	?	Yes	Mice I C	0		Only few cases described
Colorado tick fever	None Similar to dengue	Ticks	?	?	Yes	Hamster I P	0		
West Nile fever	?	?	?	?	?	Mice I C	St Louis and Japanese B	St Louis	Related to louping ill and Far Eastern virus, few cases studied

Mengo virus Isolated from mosquitoes mongooses monkeys and man in Mengo, Uganda
Ilhéos virus Isolated in Brazil Only subclinical human infections found
Semliki Forest and Bunyamvera viruses Isolated in Africa from monkeys and mosquitoes Antibodies found in human beings Can be propagated in mouse
Encephalomyocarditis virus Isolated in Manila from mild disease Can be propagated in mouse
Lot 6 virus Isolated from vaccine in the Entebbe yellow fever laboratory
Colombian viruses of Roca Garcia (Anopheles A and B, Wyeomyia Isolated from mosquitoes)

Routes of inoculation I C intracerebral I P., intraperitoneal I O intraocular

identical to the virus recovered by Armstrong and Lillie, as well as to the virus which Traub (1935) demonstrated in his colony of normal appearing white mice

According to Blackfan (1940), lymphocytic choriomeningitis in man is a benign disease It attacks both sexes As to age incidence, the patients are about equally distributed in each decade up to 40 years except during the first decade, when there are very few cases The majority of patients with the meningeal form are under 40 years of age Children are only exceptionally affected It is apparently a seasonal disease, as the majority of cases occur during the winter and spring months

In accounting for the relatively high immunity among older individuals as contrasted with the relatively low immunity of persons under 17, Armstrong and Wooley (1937) suggest that immunization of older individuals may have occurred during an epidemic seventeen years or more before, thus leaving a large number of persons under 17 years of age susceptible to infection with the specific virus

According to Blackfan (1940), while conclusive proof as to the portal of entry of the virus of lymphocytic choriomeningitis in human beings is lacking the basic evidence at the present time seems to point to droplet infection from the upper part of the respiratory tract, in both the meningeal and nonmeningeal forms of the disease A number of closely allied or identical strains of the virus of lymphocytic choriomeningitis have been described in different places throughout the United States, England, and the European continent

Blackfan (1940) stated that the onset of lymphocytic choriomeningitis often is preceded by signs referable to a minor respiratory infection, commonly called "flu" "grippe," or "cold" The symptoms usually subside before signs of meningeal irritation make their appearance—a severe headache beginning insidiously or abruptly

Lillie and Armstrong (1945), who studied the pathology of lymphocytic choriomeningitis in mice stated that the more striking gross and histologic observations in mice are polyserositis with serous exudate involving the pleura and the peritoneum Fatty degeneration of the liver, and, to a lesser extent, of the kidneys, appears as early as the third day and persists into the third week Focal necrosis occurs in the liver and, rarely, in the adrenal cortex and the corpora lutea More diffuse and irregular but sometimes focal necrosis is seen in the thymus, the spleen, the lymph nodes, and the bone marrow Scattered capillary thrombi occur in the liver and other viscera Generalized lymphocytic infiltrations, sometimes including larger lymphoid and plasma cells, some macrophages, and fewer polymorphonuclear leucocytes, involve serosal tissues of the pleura and the peritoneum, the renal cortex and pelvis, the liver, the salivary glands, the pancreas, the lungs, the heart, the adrenal glands, and less frequently, the tissue of the rest of the gastrointestinal genitourinary tracts, as well as the originally reported locations of the meninges, the choroid plexus, the ependyma, and in addition the spinal ganglia From the fact that similar visceral lesions occur not only in mice but also in intracerebrally inoculated monkeys and guinea pigs, it appeared to Lillie and Armstrong (1945) that the visceral lesions are a general effect of the virus, not peculiar to any one species Since in mice such visceral reactions appear earlier and more often after other cerebral inoculation, and since natural routes of infection are generally other than neural, it appears that spontaneous infections should produce visceral lesions proportionately more often than cerebral inoculation does and that such lesions might well dominate the pathologic picture in natural infection

Virus B	High Ascending myelitis	?	Monkeys	?	Yes	Monkey IC and IO	Related to herpes simplex and may be identical with W virus		Inclusion bodies, only laboratory infection in man
Swineherd's disease	Low Similar to dengue	?	Swine	?	During first phase	Monkey IC	0		Some claim that disease caused by Leptospira
Bwamba fever	None Similar to dengue	Mosquitoes	?	?	Yes	Mice IC	0		Only few cases described
Colorado tick fever	None Similar to dengue	Ticks	?	?	Yes	Hamster IP	0		
West Nile fever	?	?	?	?	?	Mice IC	St Louis and Japanese B	St Louis	Related to louping ill and Far Eastern virus few cases studied

Mengo virus Isolated from mosquitoes mongooses monkeys and man in Mengo Uganda
Rhôdes virus Isolated in Brazil Only subclinical human infections found
Semliki Forest and Bunyamvera viruses Isolated in Africa from monkeys and mosquitoes Antibodies found in human beings Can be propagated in mouse
Encephalomyocarditis virus Isolated in Manila from mild disease Can be propagated in mouse
Lot 6 virus Isolated from vaccine in the Entebbe yellow fever laboratory
Colombian viruses of Roca Garcia (Anopheles A and B Wyeomyia Isolated from mosquitoes)

Routes of inoculation IC intracerebral IP intraperitoneal IO intraocular

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SIMILARITIES AND DIFFERENCES AMONG MEMBERS OF LYMPHOGRANULOMA-PSITTACOSIS GROUP OF INFECTIVE AGENTS*

CHARACTERISTICS		Lymphogranuloma Venereum	Trachoma	Inclusion Conjunctivitis	Ps[illegible]acosis	Human Atypical Pneumonia [Eaton et al]	Acute Meningopneumonitis [Francis and Mag[illegible]]	Mouse Pneumonitis [Nigg]
		AGENT OF						
[illegible]ey	Elementary Bodies [125-250 mμ diam.]	+	+	+	+	+	+	+
	Cyclical Development	+	+	+	+		Probable (+)	+
[illegible]ns	Gram negative	+	+	+	+	+	+	+
	Giemsa blue to purple	+	+	+	+	+	+	+
	Macchiavello red and blue	+			+	+	+	+
	Positive Glycogen Reaction	−	+	+	−			
Primates	Ocular, Meningeal, Pulmonary, Genital, Granulomatous							
Rodent	Meningeal, Pulmonary, Hepatic, Granulomatous							
Birds	Meningeal, Hepatic, Splenic							
[illegible]r Chick	on Chorio-allantois	±	−	−	+++		++++	±
	via Yolk sac	++++	−	−	++++		++++	+++
	via Allantoic sac	±	−	−			++++	−
	via Amniotic sac	±	−	−	++++		++++	
[illegible]ate in Hem. A[illegible]		+	+	+	+	−	+	+
[illegible]tion in Complement [illegible]		+	+	+	+	+	+	
[illegible]tion in Intradermal L. V. Antigen		+	−			+		

S ff M F Jone H I a l I K M I I

Fig 138.—Similarities and differences among members of lymphogranuloma psittacosis group of infective agents (From Rake G Shaffer M F Jones H P and McKee C M Unpublished data courtesy of E R Squibb & Sons New York)

CHAPTER 22

LYMPHOGRANULOMA VENEREUM

JUAN I SOTO ROZAS

Synonyms—Climatic bubo sixth venereal disease Nicolas Favre disease bubo te inguinal lymphogranulomatosis subacute inguinal lymphogranulomatosis of intraglandular purulent foci lymphogranulomatous type of inguinal adenopathy benign inguinal lympho granuloma poradenolymphitis subacute inguinal poradenitis poradenitis subacute inguinal lymphadenitis lymphogranulomatosis inguinalis lymphogranulomatosis of the inguinal gland inguinal lymphogranuloma benign inguinal lymphogranuloma venereal lymphogranulomatosis venereal lymphopathy fourth venereal disease poradenitis nostras (Stannus Shannon 1933)

DEFINITION

Lymphogranuloma venereum is a generalized disease It is acquired like syphilis usually by sexual contact It is principally genito rectal with preference for lymphatic and nervous tissues with possible invasion of other organs such as the digestive tract respiratory apparatus cerebrospinal axis and its sheaths joints blood vessels the eye in all its segments at times the heart ovary abdominal and pelvic peritoneum spleen and skin

FREQUENCY AND GEOGRAPHIC DISTRIBUTION

The disease is frequent in Mexico Of 1 618 cases of venereal disease registered at Central Military Hospital in 1 45 3 cases (3 per cent were lymphogranuloma venereum It has been calculated that in the Mexican Army the disease is present in a proportion of 1 5 per cent In the fourteen dispensaries of the Federal District which treat venereal cases and in Morelos Hospital Mexico City there were (1945) 133 patients with lymphogranulomatosis among the 6 698 dispensary venereal patients and 87 cases among 6 653 hospitalized patients The overall percentage thus is 0 96 per cent for civilians with venereal disease

In the United States of 3 000 patients admitted to the Ant Venereal Medical Center in Hot Springs Arkansas 1 6 per cent were lymphogranulomatous according to a report by Graham (1941) covering the period between 193 and 1939

It is not possible to submit exact data on the incidence of the disease for any particular region since the means for establishing a precise diagnosis have been inadequate until very recently and because in most countries there are no regulations to compel the reporting to health authorities of cases of this disease ... For many years it was held that lymphogranuloma venereum was an exclusively tropical disease and that it had extended to temperate regions It is now known that it is worldwide in its distribution although it is most prevalent in tropical zones

ETIOLOGY

This disease was unknown before 1913 as a nosological entity and therefore many etiologic agents were described ... Durand Nicolas and Favre of Lyon published in 1913 their remarkable work ... differentiating it clinically from other venereal

SIMILARITIES AND DIFFERENCES AMONG MEMBERS OF LYMPHOGRANULOMA-PSITTACOSIS GROUP OF INFECTIVE AGENTS*

CHARACTERISTICS		AGENT OF						
		Lymphogranuloma Venereum	Trachoma	Inclusion Conjunctivitis	Psittacosis	Human Atypical Pneumonia (Eaton et al)	Acute Sheep pneumonia (Francis and Magill)	Mouse Pneumonia (Ng)
...gy	Elementary Bodies (25 250 mμ diam.)	+	+	+	+	+	+	+
	Cyclical Development	+	+	+	+		Probable (M)	+
...stics	Gram negative	+	+	+	+	+	+	+
	Giemsa blue to purple	+	+	+	+	+	+	+
	Macchiavello red and blue	+			+	+	+	+
	Positive Glycogen Reaction	−	+	+	−			
Primates	Ocular, Meningeal, Pulmonary, Genital, Granulomatous							
Rodents	Meningeal, Pulmonary, Hepatic, Granulomatous							
Birds	Meningeal, Hepatic, Splenic							
... in Chick	... Chorio allantois	±	−	−	+++		++++	±
	... Yolk sac	++++	−	−	++++		++++	+++
	... Allantoic sac	±	−	−			++++	−
	... Amniotic sac	±	−	−	++++		++++	
...ate in Host A ter		+	+	+	+	−	+	+
...tions in Complement ...ests		+	+	+	+	+	+	
...tions in Intradermal Lg V Antigen		+	−			+		

* Shaffer M F Jones H [illegible] McKee C M [illegible]

Fig 138—Similarities and differences among members of lymphogranuloma psittacosis group of infective agents (From Rake G Shaffer, M F Jones, H P, and McKee C M Unpublished data, courtesy of E R Squibb & Sons, New York)

diseases, and indicating its infectious and contagious characteristics In 1930 Sven Hellerstrom and Wassen showed that lymphogranuloma venereum is produced by a virus which is filtrable through Chamberland 13 and Berkefeld V filters It was not until 1935 that Miyagawa et al verified the existence of visible forms in tissues and secretions of infected organs The polymorphism of the agent has been verified (Coutts et al, 1938 1942 Herzberg r and Kohlmuller 1938) It was thought to follow a development cycle beginning with elementary bodies which grow multiply by division and collect in plaques and in turn into vesicles which disintegrate and release new elementary bodies which then infect new cells (Shaffer et al 1940)

Dimensions vary from a fraction of 1 micron to 4 to 6 microns exceptionally even larger Until recently the agent had not been cultivated on routine laboratory media but it had been transmitted to animals In 1930 Hellerstroem and Wassen inoculated monkeys intracerebrally in 193? Levaditi et al found the mouse to be more satisfactory Grace and Suskind (1934) introduced mouse brain antigen for use in the intradermal reaction of Frei (1925) This reaction the Frei test was originally carried out with pus extracted by aseptic puncture from softened buboes not due to secondary infection This antigen is now being replaced by mouse brain antigen and antigen made from chick embryo (Rake et al 1940, Shaffer et al 1943)

Rake and associates* noted the existence of similarities and differences between infectious agents of a group called the "lymphogranuloma psittacosis" group which includes agents of lymphogranuloma venereum trachoma inclusion conjunctivitis or blennorrhea psittacosis and human atypical pneumonia (also called virus pneumonia) acute meningopneumonitis and pneumonitis in rats (induced experimentally) Fig 138 shows the numerous similarities between lymphogranuloma venereum and psittacosis In a culture of psittacosis on chick lung violent Brownian movement was observed such as had already been seen in lymphogranuloma cultures In addition several investigators found in cultures on chick embryo that both agents (lymphogranuloma and psittacosis) have developed cycles so similar that the forms described for either could almost be mistaken for the other

The agent is susceptible to the action of sulfonamides It survives in suspensions of both brain and chick embryo in the frozen state It resists desiccation glycerin and freezing in vacuum but does not resist ultraviolet light 0 1 per cent formalin 2 per cent urea 50 per cent glycerin or ether

The discovery that individuals clinically not lymphogranulomatous react positively to the Frei test calls attention to the probable existence of a large number of latent and potentially dangerous infections in sexually promiscuous individuals However it is important to remember that a serologic relationship exists among the various agents of the lymphogranuloma psittacosis group Also on occasions when the Frei test might be of great value recent primary or secondary syphilis will give positive lymphogranulomatous reactions These reactions appear to be more sensitive than the intradermal reaction (Schaffer et al 1941) *It has been found in laboratory practice that* while the Frei test turns from positive to negative under treatment other reactions remain positive (Schaffer et al 1943) This does not coincide with observations made in our Lymphogranuloma Venereum Service in Central Military Hospital Here it has been found in a study of 22 cases (18 glandular and 4 rectal) that treatment by antigens or by sulfonamides does not influence positivity to the Frei test

*At the Squibb Research Laboratories.

Attention should be called to the vesicular reaction of Ottolina (1943) who experimented with cerebrospinal fluid concentrated in vacuum and injected intradermally This procedure produces a vesicle at the point of injection The results obtained were the same as with the Frei test

TRANSMISSION

Most frequent means of transmission is by sexual act whether normally or abnormally executed immissio penis in anum, suctio penis immissio linguae in genitalia mulieris oscula in anum alterium ejaculatio seminis alterius in os proprium semen devoret These practices whether contraceptional or perverted extend and spread lymphogranuloma venereum

In the male the primary lesion Bory chancre (Bory, 1921) is generally in the penis meatus or anterior urethra In the female it may be in the vagina cervix of the uterus labia majora and labia minora The localization of this lesion explains the gland invasion which follows as will be seen later

In the passive pederast the initial lesion is localized in the anus or in the rectum Coutts et al (1940) have cited cases of Bory chancre of the lips tongue and pharynx with cervical adenopathy lymphogranulomatous cheilitis marginal glossitis tonsillitis pharyngitis and laryngitis Perhaps the ingested microorganisms can cause lesions in the entire digestive tract

Other organs which may be affected include the spleen liver, eye (Coutts and Espildora 1934) by direct inoculation or by general invasion respiratory system (lungs) joints the cerebrospinal axis (Sabin and Aring 1942) perhaps even the heart and arteries (May 1944) and also the skin (Kleber 1930)

Laboratory workers have been infected by the sneeze spray of infected experimental animals In other cases the organism has penetrated through the skin on the hands (Harrop et al 1941)

PATHOLOGIC ANATOMY

Bory chancre is a plasmoma without polymorphonuclears with newly formed blood vessels near the surface, this distinguishes this chancre from the primary lesion of syphilis and from soft chancre

Microscopically the epidermis is thickened as are also the interpapillary prolongations papillae becoming thinned out there is infiltration between epidermis and dermis principally of polynuclear leucocytes filling the edematous epidermis Vessels are dilated with cells and intercellular spaces in edematous condition the clear limit between the epidermis and the Malpighian body cannot be seen the number of spindle cells is increased and they are in a state of division According to Favre (1930) there are no polymorphonuclears in the pathologic fluid for which reason he called the lesion a "plasmoma" In the center there is a microabscess similar to microabscesses of the glands in the walls of which are found epithelial cells polymorphonuclears and acidophilic mononuclears in great abundance, which enclose the Gamna corpuscles (Gamna 1923)

diseases and indicating its infectious and contagious characteristics In 1930 Sven, Hellerstroem and Wassen showed that lymphogranuloma venereum is produced by a virus which is filtrable through Chamberland 13 and Berkefeld V filters It was not until 1935 that Miyagawa et al verified the existence of visible forms in tissues and secretions of infected organs The polymorphism of the agent has been verified (Coutts et al, 1938 1942, Herzberger and Koblmuller 1938) It was thought to follow a development cycle beginning with elementary bodies which grow multiply by division and collect in plaques and in turn into vesicles which disintegrate and release new elementary bodies which then infect new cells (Shaffer et al 1940)

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*At the Squibb Research Laboratories

Genito ano rectal lesions (*Jersild's syndrome*) are characterized by elephantiasic edema which deforms the organ In some parts these are infiltrated with tense superficial covering while in other parts there may be deep sclerous ridges There are hard or soft nodules fistulas indiscriminately scattered dry or suppurating In the female the vagina may be intact with at times slight infiltration If the rectum is invaded initial lesions are simply inflammatory later becoming sclerotic (cicatricial) with narrowing of the diameter of the organ generally in the area of from 3 to 4 cm from the anal

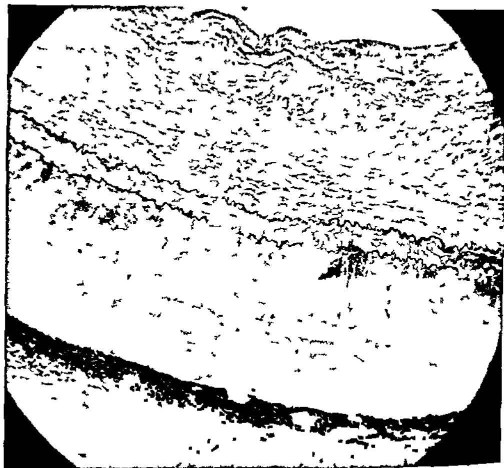


Fig 140—Marked endarterial thickening duplication and lack of continuity of internal tunica elastica (Photomicrograph by Mayor M C L Contreras R collection of Soto)

sphincter to about 8 or 10 cm that is the stenosis corresponds to the region of the glands of Gerota which in the female are anatomically located at this point Proctoscopically we observe red and violet colored mucosa edematous sometimes ulcerated vegetative and stenotic

Microscopically the lesions are such as are present in all forms of elephantiasis sclerosis new formation of connective tissue edema cellular infiltration vascular lesions granular tissue with enormous infiltration of leucocytes and plasma cells In some cases the infiltration is perivascular in others it resembles

Microscopic lesions in gland tissue show increased volume or glands adherent to each other and to surrounding connective tissue which is found to be infiltrated and hardened On extirpation there is obtained a hard fibrous mass softened in some portions and very vascular Superficial glands are small hard and reddish the inflammatory tissue which follows consists of large also hard wine colored masses with small abscesses in the center are two or more enlarged glands yellowish white and soft containing numerous microabscesses In sections we see fibrous filaments outlining small cavities filled with serum and pus In the interglandular tissue abscesses also exist with this difference they are larger and generally fistulous

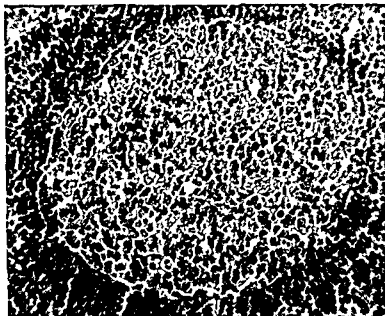


Fig 139 —Lymphocytic plasmocytic infiltration of connective tissue (Photomicrograph by Mayor M C F Contreras R collection of Soto)

Microscopic sections reveal the microabscesses limited by the epithelial cover In the glands can be distinguished the external cortical zone the internal cortical zone the intermediate zone and the central zone In the external cortical zone small nests of macrophages are found these have large *nuclei poor in chromatin* The *internal cortical zone* is a *fibrous skeleton* which forms large alveoli in the depth of which are found polynuclears lymphocytes and connective tissue cells The intermediate zones present multiple cellular elements remnants of polymorphonuclear leucocytes with fibrin among them The central zone is composed of unrecognizable cellular fragments made up of small clusters irregular oval round or elliptical scattered in a fibrous sheath Some of these elements have pyknotic nuclei (Phylactos 1922)

teristics help but little in making an early diagnosis in most cases since this type of lesion is not the most frequent (9 per cent) The most frequent form is the herpetiform chancre (73 per cent) which as the name implies looks very much like herpes with which it may be confused because of its ulcerative manifestations It is a very small chancre of brief duration sometimes fleeting so that unless the physician finds traces of it or unless the patient tells of having had the ulcer one might suppose that the adenitis was the beginning of the morbid process (bubo d emblee)

Next in frequency is the syphiloid form (12 per cent) This is so much like *a primary syphilitic lesion that according to Sezary it is frequently con*fused with it until typical adenopathy makes its appearance and establishes the differential diagnosis The syphiloid chancre an ulceration with an indurated base persists for several weeks when left to itself



Fig 14ª—Fluctuating lymphogranulomatous bubo (Photograph by O Pérez collection of Soto)

The chancriform type may be confused with soft chancre because of the *irregular ulceration with a soft base which heals in several* weeks leaving a scar It has a frequency of 6 per cent

Finally the infiltrating Bory chancre has the lowest frequency (3 per cent) according to Sézary Below the skin or mucosa which may be normal in color or reddish an infiltrated area may be noted upon palpation *It varies* in form and in dimensions may be thick or thin and the contour may be either regular or irregular

Bory chancre appears usually 20 to 40 days after inoculation The incubation period may however be shorter (8 to 15 days) Duration of the chancre depends upon various factors treatment virulence of the infectious agent infiltration of the lesion natural defenses of the patient It may be fleeting or it may last for weeks or even months

tuberculous follicles There are epithelial cells, giant cells surrounded by lymphocytes, and numerous plasma cells This process invades the dermis and cellular tissue, where we find edema, infiltration, and sclerosis The lymphatics are dilated and contain numerous lymphocytes and plasma cells Even when there is no elephantiasis, but only ulceration, there are always signs of sclerosis lymphangitis, and vascularitis, just as in elephantiasis

CLINICAL FORMS

Like syphilis, lymphogranuloma venereum also presents the primary lesion or chancre of inoculation and, later, various lymphatic, mucocutaneous, vascular, visceral osteoarticular nervous etc localizations so that this disease also presents the picture of general infection

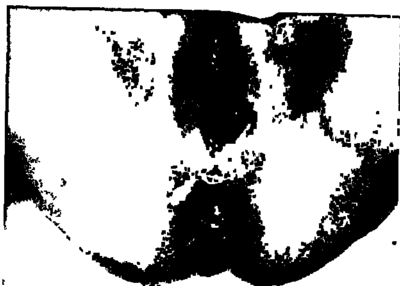


Fig 141 —Cicatrix of femoral ligature and extirpation of lymphogranulomatous glands (Collection of Soto)

The initial lesion or Bory chancre (Bory 1921 1924) presents unmistakable characteristics in its typical form, however it is frequently confused with soft chancre, the primary lesion of syphilis mixed chancre (Ducrey syphilis), or other venereal diseases Often this infection does not occur alone but simultaneously with another venereal disease (in association with the soft chancre of Ducrey, with syphilis, or with gonorrhea)

Sezary (1935) classified the initial lesion, on the basis of its appearance, into herpetiform, syphiloid and nodular chancres with three subtypes pure nodular, ulcerated and follicular nodular chancriform (like Ducrey's soft chancre), infiltrating

Pure nodular chancre is characteristic a rounded nodule 5 to 10 mm in diameter, painless but little inflamed firm, covered by normal colored or slightly pink mucosa, and lasting several weeks Unfortunately, these charac



A



B

Fig 143 —*A* *B* *C* Invasion of genitals and anus (Jersild syndrome) *D* Vulvar elephantiasis Perineal anal invasion (Photograph by O Peréz)

Although the most frequent localization of the initial lesion is on the penis it may also localize in the meatus the urethra the anus or the rectum or as in syphilis it may be extragenital

Meatitis described by Coutts presents a reddened meatus edematous and infiltrated generally to a moderate extent at times more or less inflamed Urethritis appears as mild (urethritis of Waelsch?) and asymptomatic showing a thin whitish or whitish yellow discharge with a few shreds in the urine collected in the first vessel Leucocytes epithelial cells and mucus are found No bacteria are seen but the secretion may be antigenic since it contains Miyagawa corpuscles or their products

The infection may spread from any of these initial lesions along the corresponding lymphatic vessels to the inguinal and iliac glands on both sides resulting in formation of various changes according to the location If it occurs in the lymphatic vesicles of the penis (truncal lymphangitis of May 1940) it is palpable It may form an abscess which discharges and leaves a fistula Another important sign described by May as quite frequent is what he calls early regional edema This is due to obstruction of lymphatic circulation and to lymphangitis When it localizes in the prepuce which becomes violet in color this author calls it violet edema of the prepuce According to other authors it may occur later as a sign of further outbreaks of the disease and should be looked for moreover in the penoscrotal angle in the pubis or hypogastrium and in the muscle (femoral triangle)

Within 1 to 6 weeks after the appearance of the Bory chancre we see inguinal adenitis unilateral or bilateral The tumor like mass is ovoid varying from the size of a pigeon egg to that of a turkey egg In some cases however the adenitis precedes by several days the Bory chancre or d emblée appears without this antecedent adenitis Inguino iliac adenitis may present various forms from syphiloid to abortive and may develop suddenly or slowly

The patient experiences discomfort on one side of the groin or both on walking Glands are slightly enlarged hard isolated with one larger than the others with little or no pain (syphiloid adenopathy) A few days later periadenitis appears which unites the glands resulting in a hard formation which adheres to the skin This may extend toward the iliac fossa and embrace the iliac glands (in one third of the cases) constituting according to Sézary the pathognomonic sign Or it may extend toward the anterosuperior iliac spine and invade all the inguinal glands or toward Scarpa s triangle including the inferior or external group and the central glands (inguino central form)

In about one third of the cases this adenitis is bilateral It frequently begins on one side and then passes to the other with different characteristics Two to four weeks later the signs and symptoms are characteristic and well defined

1 Palpation with pressure upon these glands in spite of the appearance of acute inflammation elicits no pain (Favre s sign of glandular disturbance)

2 The entire mass can be moved *upon a deep plane* ("shaking sign" of Favre)

3 Color of the skin *changes from reddish to violaceous* (violet adenitis of Favre)

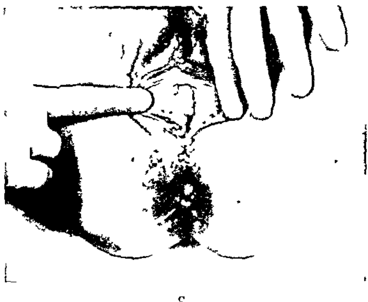
4 The periadenitis *upon infiltration of cellular tissue* gives a sieve like aspect to the mass (" accompanying cellulitis " of Favre)

5 When the *tumor like mass is palpated* softened spots are found in the midst of the hard mass these are small intraglandular or periglandular collections which *remain isolated* ("*suppurating pockets with hard margins*" of Favre 1931)

When these abscesses open spontaneously they leave multiple fistulae with thin viscous gummy serosanguinolent yellowish or whitish secretion *The intermediate* skin generally remains intact However there are cases in which this process is confused with adenitis due to soft chancre This con*fusion is caused as much by* the quantity as by the character of the pus (*sup puration in mass of Pautrier 1924*) If left to itself the adenitis terminates *in atrophy of the glands and in sclerosis* (after several months or even years) During the course of development of the adenitis various lesions can be found *in the same tumor like mass ranging from definitely hard all the way to* fistulas perforating through the softened areas At times (Soto 1945) al*though rarely the process invades the femoral vessels resulting in hemorrhage* and perhaps in death if application of a ligature does not stop the loss of blood *in time*

At times the infectious agent invades the genitourinary organs as a form *of lymphogranulomatous epididymitis* (Coutts) *with localization in the tail* which most frequently develops fistulae Or the invasion may take the form *of ulcerative leucoplastic or vegetating lesions in the urethra terminating* in most cases in stenosis of the canal These lesions may extend to the pos*terior urethra and to the vesical neck presenting corresponding* symptomatology (Baneiu Coutts and Opizzo 1939) In the genital apparatus further spread *appears later genital elephantiasis involving* the external organs male and female due to obliteration of superficial lymphatic vessels and invading the labia *majora and minora in the female* and the prepuce or the entire penis and even the scrotum in the male Sequelae in the male may be a continuation of the Bory chancre of a bubo an inguinal fistula or plastic induration of the penis (May 1940) with nodules or fibrous plaques in the median dorsal line of the penis in the septum intercavernosum These formations are due simply to Miyagawa corpuscles which are carried directly to the region by the lymphatic route or which proceed by continuity from urethritis littritis and periurethritis of the same origin May found CF positive results with the Frei reaction in 85 cases of this disease Finally the invasion may take the form of urethroperineal or urethrorectal fistulae accompanied by urethritis peri urethritis genital elephantiasis and at times rectal stenosis (vulvar esthiomene and Jersild s syndrome)

Rectal invasion may be a direct infection from abnormal sexual practices it may be an indirect infection from secretions clothing utensils *instruments*,



C



D

Fig 111 (Cont'd)—For legend see opposite page

The process begins with all the symptoms and signs of acute rectitis the etiologic diagnosis of which is of enormous importance If subjected to intense specific treatment *the disease can be cured in the majority* of cases and rarely develops into chronic ulcerative or vegetating forms or the stenotic form Aravantinos (1935) reiterates the importance of diagnosis and states *that the Frei test is indispensable* for every patient with acute rectitis The chronic ulcerative form the infiltrated or vegetating form lasts for several years In the majority of patients from 20 to 50 years of age the disease terminates with a stricture of the rectum which in the beginning is inflammatory and then cicatricial If not treated the prognosis is fatal Generally some intercurrent affection (cachexia and tuberculosis pyelonephritis bronchopneumonia) at times a complication (intestinal occlusion perforation of the intestine and peritonitis) results in death

Since this is a *general infection fever occurs irregular in most cases* it seldom reaches 40° C and occasionally passes unnoticed Other general symptoms common to all infections are anorexia prostration loss of weight *headache anemia etc*

There have been described rheumatoid painful manifestations arthralgia and cutaneous eruptions—the polymorphous and nodular erythema type scarlatiniform urticariform ecthymatiform pruriginous rash furunculosis hard nodules which soften resulting in fistulae which can be classified as lymphogranulomatous chancres

OTHER LOCALIZATIONS

Kitagawa (1934) on ophthalmoscopic tests of the eye in *thirty lymphogranulomatous* patients found peripapillary edema and dilatation and tortuosity of blood vessels in most of the cases American European and Japanese authors have identified the symptoms and signs found in lymphogranulomatosis with the oculoglandular syndrome of Parinaud Appelmans referred to the case of a young physician who was accidentally infected at the University of Louvain The Frei test was made repeatedly and gave constantly positive results Coutts and Sanders published the case of a patient with the oculoglandular syndrome of Parinaud in whom the Frei test was intensely positive and who improved rapidly under sulfonamide therapy Inoculations were made from a fragment of the diseased conjunctiva into the brains of a monkey and mice Antigens obtained from these tissues gave positive reactions in patients with lymphogranulomatosis (See Oliphant et al 1942)

McNie (1942) of New York discussed the same subject and stated that the disease was lymphogranulomatosis This could be demonstrated perfectly since Miyagawa corpuscles were found in the posterior surface of the cornea *in eyes experimentally infected* with the aqueous humor taken from patients with Parinaud s syndrome

Vergara Espino in an informal verbal communication before the Society of Gastroenterology *stated that the reddening of the papilla* which he

fingers, etc., or it may be a later complication of an old and forgotten Bory chancre or of a lymphogranulomatous meatitis or urethritis. With reference to the direct infection Quiroga (1940) published the results of investigations in collaboration with Lanza and Zuccari made in a prison in Buenos Aires. He made Frei tests on 100 prisoners, 20 of whom were pederasts. The results were positive in 7 cases of each group. In the normal group it was possible to find scars of old inguinal lymphogranulomatoses. In 7 sodomy habitues there were rectal manifestations of a lymphogranulomatous character which were not seen in any of the normal subjects. However, it is not to be assumed that every rectal lymphogranulomatosis is proof of pederasty. Bensaude, the *wizard of rectoscopy*, as he is called in Paris, and Lambling state that more than four fifths of such patients are passive pederasts (1934).



Fig. 144.—Jersild syndrome: genito-ano-rectal lesion; stenosis of the rectum. (Photograph by D. Pérez, collection of Soto.)

In these cases infection penetrates across the mucosa by excoriation or by simple inflammatory lesions to the lymphatic network of the rectum. The tissues first invaded are the submucous and the intramuscular; next involved is the tissue between the rectum and the perirectal fascia or the peritoneum; and finally tissue is involved which could be called extramural, around the rectal wall, which communicates with the glands described by Gerota 3 to 8 cm. from the anus. Great importance has been assigned to infection of the glands of Gerota, but at the present time Lavre states that rectal infection is very little adenophilic.

In addition to lymphangitis and adenitis there may be lesions of blood vessels (arteries and veins) and local inflammatory lesions which, acting upon one another, lead to similarity with ulcers and sclerosis production (Cohen, 1930). Savignac (1937) calls this form of rectitis "chronic stenosal venereal rectitis" because in many patients other venereal diseases exist, such as syphilis, soft chancre and gonorrhea.

In forms which have persisted for several months localization occurs i the joints in approximately one tenth of the cases The joints most frequentl invaded are in the order of frequency the wrist fingers elbows the ankle and the knees (Grace 1941) In some cases there is articular damage wit reddening and great sensitivity of the skin covering the region The artic lar elements are not destroyed however, and the function of the joint eventually completely restored when the disease has been cured althoug the resultant arthritis may persist for years or may at times cause invalidis if the disease itself has not been properly treated

During the period of invasion lymphogranuloma venereum present general phenomena which vary in different patients All however confir the fact that we are dealing with a generalized infection Among the mos frequent indications are headache fever chills sweating anorexia nausea vomiting weakness loss of weight and prostration Also common are mus cular pains and a feeling of tenderness in the muscles arthralgia rheumatoi pains both in active or passive movement either accompanied by or withou swelling or inflammation of the throat conjunctivitis or generalized rash

DIFFERENTIAL DIAGNOSIS

Lymphogranuloma venereum as with most genital infections may b acute or chronic Both forms may be confused with many local or genera febrile conditions because of the similarity of signs and symptoms for ex ample in acute affections of the digestive and respiratory systems The disease may be confused with other venereal diseases with tuberculosis Hodgkin s disease lymphatic leucemia tularemia filariasis actinomycosis dysentery ulcerative colitis etc

Table XV is a summary of the most important differential characteristics of some diseases which most frequently make the diagnosis of lymphogranu loma venereum difficult

LABORATORY FINDINGS*

The Frei test the complement fixation test and the Miyagawa corpuscles regarded as the organism of the disease have already been considered

The intradermal test of Frei is positive only at the peak of the allergic period that is when specific antibodies have been formed in the infected or ganism This usually occurs only about 2 weeks after inoculation although at times it can occur later so that it is not difficult to understand that the test is negative at the beginning of the disease The test may also give neg ative results during the menstrual period and in the not so rare cases of floral syphilis when the two diseases exist in the same patient at the same time It is said that the test remains positive for the duration of the patient s life

Interpretation of results should be made from the fourth day According to Sulkin (1941) the reaction appears in 24 to 48 hours reaching a maximum in 3 days after which it gradually decreases in intensity A positive reaction

*Antigens may be obtained from E R Squibb and Sons

had observed was due to mild neuritis without serious effect upon the field of vision or upon the acuteness of vision

In 1928 a case at the General Military Hospital was studied by the Chief of Ophthalmological Service the then Col M C Adolfo Viguri Viguri The patient a 45 year old woman had unmistakable antecedent history of inguino crural glandular lymphogranulomatosis About a month after the development of the disease disturbances in the left eye began oculopalpebral con*gestion sensation as if there were particles of sand in the eye, abundant yel*lowish suppuration and conjunctivopalpebral growths (papillomatous neo formations in crest like groups) principally in the lower eyelid which were not modified by antigenic treatment Harrop Rake and Schaffer (1941) described two cases of nasal laboratory infection from the sneeze-spray of in*fected rats Septic fever with chills was observed with sweating articular* rheumatism and headache pharyngitis or laryngitis and adenopathy of the neck These authors refer to another case in which infection occurred through the skin of the hands

Cases have been described of accidental infection of surgeons who later developed buboes in the axilla (Klotz, 1890) Primary lesions have been described on the tongue of one patient 3 weeks after he had practiced cunnilingus *Two small lesions appeared on the side of the tongue* and five weeks later a voluminous tumor developed in the neck glands (Stannus 1933) Chronic chapping of the lips thickening of the tongue, and cheilitis in persons who had practiced coitus ab ore have been described by Coutts and other venereologists as have glossitis marginata and lichen produced by the *agent of lymphogranulomatosis which also causes tonsillitis pharyngitis and* laryngitis Milian has reported cases in which aphthae and buccal and genital lichen were found together Brulé (1937) in Paris and Coutts in Valparaiso described myositis of the nucha in patients practicing suctio penis who presented the genito ano rectal syndrome of Jersild Coutts also observed *two cases of plastic linitis of the stomach with positive Frei test two cases of* lymphogranulomatous patients with ileo lentis and periduodenitis and other patients with duodenal ulcer

In addition Crohn et al found terminal ileitis also called regional enteritis to be a granulomatosis This may affect not only the small intestine but also the large intestine and might be confused with appendicitis (Crohn et al 1932) because of the pain and palpable swelling in the right iliac fossa Left alone it may lead to acute obstruction perforation of the intestine and formation of fistulae which open into the abdominal viscera or into the abdominal wall These cases were almost always found among young persons be*tween 20 and 30 years of age*

Goodman (1936) found ulcerative colitis and stenotic lymphogranulomatous colitis in the ascending transverse and descending colon Cases of meningoencephalitis have also been described (Sabin and Aring 1942) and spinal fluid from patients with lymphogranulomatosis has been used success*fully as antigen in the Frei test (Aleman Pérez)*

consists of a papule vesicle or pustule with a diameter larger than 6 mm (Grace 1939) According to our observations the reaction persists after the *fourth day* for several weeks A corresponding subject should always be used in carrying out the test so that unspecific reactions will be eliminated for these have a maximum diameter of only 6 mm and decrease after three days

The reaction is more intense in inguinal than in rectal cases it seems that the attack upon the skin by the infectious agents influences this

Although some investigators have obtained better results by *using mouse* brain antigen most of the American workers (Sulkin Rake and Grace and Greenblatt 1941 Mortara and Greenblatt 1943 Axelrod 1942) agree that *the chick embryo antigen Lygranum is superior to all others* for use in the Frei test and that this antigen constitutes a more satisfactory procedure in the diagnosis of lymphogranuloma venereum In a study made by our Service (Gonzalez *Tasso* 1941) of 105 cases at Central Military Hospital we reached the same conclusion

The sole disadvantage of this test is its delayed appearance Ravaut et al (1932) proposed a hemo reaction for an early diagnosis An active antigen is injected intravenously this produces a temperature of 39° to 40° C after 12 to 18 hours The fever remains for 24 to 48 hours and is accompanied by general malaise chills headache insomnia weakness arterial hypotension and leucopenia This test has one disadvantage it can be used only once A second test on the same patient with the same quantity of antigen gives a weaker reaction and it is necessary to give twice or four times the usual dose to obtain the same results Continued injections eventually have no effect It *is stated that this test is negative in all patients who are not carriers* of the lymphogranuloma agent which would give the test a specificity of 100 per cent Regarding its sensitivity (Flandin and Turiaf 1936) the test is positive in 97 per cent of the cases

As for the complement fixation test we repeat that in both primary syphilis and in neurosyphilis these tests may give false positive results The intradermal test made with a good antigen is of greatest value in these cases On the other hand lymphogranulomatous patients may exhibit false positive reactions for syphilis (Heyman and Webb 1946) The practical advantages of the complement fixation test are its simplicity rapidity the small quantity of serum required (1 6 c c) and its appearance one week after initiation of the symptoms The test can be carried out at the same time and with the same tube of serum as the test for syphilis made before marriage The patient is not required to return to the laboratory as he must for the intradermal test It appears then in general that this test would be more useful for learning the incidence of the disease among the general population since positive cases could be submitted to clinical examination and to the intradermal test This *would place a large number of cases of* lymphogranuloma venereum under sanitary control Most of these cases are unrecognized at the present time

The test for the neutralization power of the patient s serum (Levaditi et al 1932) has not as yet come *into common use The presence of* Miyagawa

DISEASE	ETIOLOGY	INCUBATION PERIOD	INITIAL LESION	INGUINAL ADENOPATHY	SPECIFIC TESTS
Lymphogranuloma venereum	Virus	Approximately 15 days	Herpetiform papules may be unnoticed	Generally unilateral (left sided), inflammation the size of fist or larger, reaches several glands, painful, characteristic violaceous discoloration of the skin, suppuration is frequent, fistulae are multiple, substance aspirated from the fluctuant glands does not contain bacteria unless secondary infection exists	1. Frei test with human, mouse brain, chick embryo antigens. Complement fixation test with chick embryo antigen
Syphilis	Treponema pallidum (Spirochaeta pallida)	[illegible] to 6 weeks	Characteristic soft chancre, hard-rimmed papules, appears at first as an umbilicated papule	Characteristic "Ricord's pleiades," glands of definite consistency, acute inflammation generally does not exist, suppuration very rare	1. Wassermann test. Kahn test. 3. Dark field examination may show treponemata*
Soft chancre	Hemophilus ducreyi	3 to 8 days	Painful ulcer with granular base, abundant pus, bleeds readily, lesions may be multiple due to autoinfection	Glands enlarge in approximately one third of cases, usually with acute inflammation, bubo often painful and tends to suppurate, forming one fistula	1. Ducrey bacillus found in the lesion. Ito-Reenstierna test positive
Gonorrhea	Neisseria gonorrhoeae	3 to 5 days	Characteristic urethritis with profuse suppuration	Generally appears after termination of urethral suppuration, may be unilateral or bilateral, rarely suppurates	1. Typical diplococcus found in pus. 2. The microorganism may be cultivated
Tuberculosis	Mycobacterium tuberculosis (Koch's bacillus)	Insidious	May be of three forms—(1) ulcer with excavated borders, miliary tubercles may be seen at its base, (2) with nodules of characteristic apple jelly appearance, (3) indurated lesion with fistulous apertures	Hard with well-defined inflammation, growing slowly and adhering to skin, glands open through simple or multiple fistulae discharging pus	1. Bacillus tuberculosis in pus. Biopsy shows characteristic tubercles. 3. Tubercle bacillus may be injected into animals experimentally
Inguinal granuloma	Donovan bodies	3 to 6 weeks	Ulcerated papule extends in serpiginous form, forms cicatrix in center, extending to periphery	Inguinal lymphadenitis occurs only when secondary infection of the initial lesion exists	Donovan bodies found in scrapings from lesions, pathognomonic cells with foamy cytoplasm containing cysts of Donovan bodies may be seen by using Wright or Giemsa stain
Malignant tumor	Etiology unknown	Insidious	Epithelioma appearing generally in patients past 40 years of age, granular ulcer which bleeds freely with hard base	Characteristic malignant invasion	Biopsy shows character of the malignant tumor

Some success on a lesser scale was obtained with sodium salicylate (Chevalier and Fichrer) iodine (Ravaut) xylol administered orally in capsules (Menéndez in El Salvador) copper ammonium sulfate (Carré) and injections of gold (Almquist Lepinay Kalz etc) before the era of the sulfonamide drugs

Early in 1938 attempts were made to evaluate the therapeutic power of the sulfonamides in the different clinical types of this disease In 23 cases of lymphogranuloma Gjuric (1938) successfully used continuous treatment with Fuadin and Prontosil and recommended an ointment containing 10 per cent *Prontosil* to be applied to the open bul oes Later many other authors tried various sulfonamides both on human beings and on laboratory animals notably guinea pigs and mice It was found that treatment of the laboratory animals with sulfonamides (Findlay 1940a and 1940b) reduced mortality rates from 84 to 49 per cent if the animals had received sulfonamide daily in their food

It was observed however that in practically no case did rats remain indefinitely free of all symptoms whether they had been treated or not This observation is important because in spite of the sulfonamide treatment the majority of patients persist in showing positive Frei tests and positive complement fixation reactions which indicates that the infection probably is still present in latent form and these individuals have been converted into the highly dangerous carriers (Jones et al 1941)

Several studies have been carried out to determine the therapeutic value of various compounds It may be stated that in vitro as in vivo sulfadiazine holds the first place in treatment followed by sulfathiazole sodium sulfanilate sulfaguanidine and sulfanilamide

Chloromycetin has been used with some success in this disease This product was initially obtained from a new species of soil organism isolated in Venezuela now designated as *Streptomyces venezuelae* It is identified chemically and is the first antibiotic to be produced synthetically on a practical basis *Chloromycetin in a dose of 1 0 Gm* every eight hours for 14 days has induced clinical cure although the elementary body may still remain demonstrable in the tissues

Since 1940 (Grace 1941) sulfathiazole has been used at the Grace Clinic in the following manner 1 5 Gm that is 3 tablets of 0 50 Gm each are given three times a day for two weeks for a total dosage of 4 5 Gm daily During the three following weeks 1 Gm or 2 tablets are given in the same manner The treatment is discontinued for 3 weeks and is then repeated for 5 weeks This 5 week period is not always necessary to terminate the treatment In lymphogranulomatous ophthalmia *sulfadiazine* (Oliphant et al 1942) has been used as follows 3 Gm (6 tablets) divided into 3 doses daily for 5 days with 3 days of rest then repetition of the treatment The patient is considered cured after he has taken 30 Gm of sulfadiazine Sulfanilamide has cured 80 per cent of inguinal cases in 6 weeks and the remaining 20 per cent in 16 weeks with a total of 52 Gm Rectal cases re

corpuscles in infected tissues as seen in secretions is to be considered diagnostic of the disease These corpuscles can be seen microscopically with certain stains—eosin methylene blue Macchiavello Giemsa Noble Inoculation of mouse brain and chick embryo may also be carried out to facilitate the search

The Schilling differential count should also be mentioned In our study results were as follows leucocytosis 77 per cent, decrease in red blood cells 55 per cent neutrophilia 41 per cent lymphopenia 45 per cent monocytopenia, 41 per cent Hyperglobulinemia was found in 48 per cent of the patients and hyperproteinemia in 16 per cent

TREATMENT

Treatment of this general infection is medical no matter what organs are attacked Quinine was used in 1879 in Hungary in the belief that malaria was being treated Prior to 1927 localizations in the glands were surgically handled while rectal lesions were confused with syphiloma ' of Fournier and the external genital lesions especially in females were confused with elephantiasis and so called 'esthiomene" of the vulva In 1921 Ravaut and Scheikewitch discovered certain lymphogranulomatous formations in pus and mistook these for amebae They treated 4 cases of gland fistula with emetine and obtained favorable results Ravaut (1921) concluded that emetine had cured his patients Rodriguez Meza (1936) in Mexico tried the treatment At the present time however it has fallen into disuse

In 1923 in Argentina Destéfano and Vaccarezza (1927) introduced tartar emetic in the form of intravenous injections The results were good This preparation has certain objectionable features it is unstable it is toxic and it is not well tolerated by some patients (nausea vomiting vertigo general malaise chills cough intense pain throughout the length of the injected member and later intense polyarticular pains muscular pain and general debility) For this reason other salts have been sought Neoantimosan was later named *Fuadin* Other products are Neostibosan Neostam and in France in 1934 Anthiomaline (lithium antimony thiomalate) (Sézary and Lacquet 1934)

Neostibosan has given better results than Fuadin (Lopez Fagelking 1934) Polak (1933) reported cures using Stibial Hissard (1933) reported cure of 2 cases of urethritis which he called benign subacute since the Frei test was negative

According to Laurens (1935) Anthiomaline administration cured 50 per cent of the cases or its use resulted in great improvement conducive to cure In 26 per cent of the cases partial improvement was effected, while in only 14 per cent fistula formation could not be avoided

It may be concluded then that preparations of antimony constitute excellent medication for this disease but the treatment is inconstant and fistula formation and recurrences induce one to believe that the treatment is not specific

"*Sulfavibus* (for local infiltration) 10 c c daily taking into account that this amount is equivalent to 3 Gm to be combined with oral treatment keeping in mind the patient s tolerance

"*Intramuscular Antigenfabre* (smaller doses must be used for intravenous injections) Initial dose 0 25 c c maximum dose 2 c c or more according to tolerance With reactivation of lesions dilute in physiologic saline 0 75 c c of saline for every 0 25 c c of antigen Apply two or three times a week (In Central Military Hospital up to 140 c c of Antigenfabre have been used) (Soto• 1945)

'*Repodral* Initial dose 3 5 c c continue with 5 c c until a total of 10 or 15 injections have been given After a rest period of 30 days (accumulation) another equal series may be used Never to be used simultaneously with sul fonamides (Peryassu 1939 reported good results) unless antigen therapy can be applied "

Manifestations of the disease to be treated are (1) abdominal iliac in guinal adenopathy (2) acute or chronic nonstenosing rectitis (3) chronic stenosing rectitis (Other localizations have not been considered in these soldiers although such localizations are frequently present in their associates)

Adenopathy should be treated with sulfathiazole and with antigen therapy (minimum treatment of one month) If it does not yield to treatment the affected tissues are infiltrated with 10 c c of Sulfavibus daily (Fluctuating buboes are to be punctured and a volume of Sulfavibus equal to the amount of extracted liquid is to be used)

Chronic rectitis not stenosing should be treated in the same manner except that in acute phases 2 Gm of sulfasuxidine instead of sulfathiazole are administered every 8 hours and a daily infiltration with Sulfavibus of the accessible affected parts is practiced with due regard to tolerance until clinical cure has been effected (In all cases of open lesions including rectal lesions surgical sulfathiazole powder should be applied)

Chronic stenosing rectitis Patients must be sent to a hospital for surgical treatment This consists of resecting the stenotic rectum with or without prior colostomy or simply making an artificial anus according to the state of the patient (Borjas 1942)

Jersild s syndrome and elephantiasis in women are treated by infiltration and by surgery carrying out the indicated operations in each case

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quired 10 months with a total of 172 Gm to cure 39 per cent of the patients In one case 584 Gm were administered in the course of a year, without results

Gray and Barnes (1940) tried injections of Frei antigen subcutaneously and intradermally with good results Grace (1941) used intravenous injections Prats (1939) used the same method of treatment but also used sulfonamide simultaneously The number of satisfactory results rose from 56 to 92 per cent Finally Bercovitz (1940) achieved success with intensive subcutaneous treatment He injected the antigen every 5 days increasing the dose from 0 1 c c up to 1 0 c c Best results have appeared in cases of rectal obstruction although slowly and gradually Treatment should last at least a year but the patient must be under observation for a much longer period

Kalz (1932) and Kalz and Sayler (1933) used injections of serum from lymphogranulomatous convalescents with better results than with Solganal radium therapy Neostibosan or surgical treatment On our Service blood injections from the patient himself as well as from other convalescents have been utilized rather successfully (Cruz Martinez 1939)

Sulfonamides have also been used parenterally Aleman Perez (1943) who originated the method in our country used first soluble sulfapyridine (Streptocid) then para aminobenzol sulfamido methylene sulfoxylate of sodium (Deseptyl) and last 30 per cent sulfamido succinate of sodium (Sulfavibus) at pH 7 0 The maximum injected dose of Streptocid was 3 Gm of Deseptyl up to 6 Gm and up to 9 Gm Sulfavibus were used in one injection It is necessary at the beginning of the treatment at the time of application to mix the product with cocaine to prevent pain (novocain must not be used because it forms a combination which may diminish the activity of the compound) Injections are made twice a week A decided improvement is observed after 6 or 8 injections Aleman Pérez treated 30 female patients with satisfactory results On our Service 50 patients with various localizations have been treated to date with very good results

The following therapeutics are used in the Mexican Army sulfathiazole sulfasuxidine sodium sulfamidosuccinate 30 per cent (Vibus Laboratories Mexico D F) Frei antigen for treatment called Antigenfabre (Vibus Laboratories) composed of a solution of infected mouse brain with the globulin mucoproteins and scleroproteins removed Antigenfabre in the form of an amino acid compound is dispensed in 10 c c ampule vials Norms have been established for the use of these products* and have been sent to all Military physicians of the Republic

Sulfathiazole Initial dose 0 10 Gm multiplied by 1/6 of the patient s weight Total dose in 24 hours 0 10 Gm multiplied by 2/3 of the patient s weight

Sulfasuxidine Initial dose 0 10 Gm multiplied by 1/3 of the patient s weight Total dose for 24 hours 0 10 Gm multiplied by the weight

*Oficio Circular Sanidad Militar Dirección Oct 1 1944 México D F

"*Sulfavibus* (for local infiltration) 10 c c daily, taking into account that this amount is equivalent to 3 Gm, to be combined with oral treatment *keeping* in mind the patient s tolerance

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CHAPTER 23

GRANULOMA INGUINALE

Robert B. Greenblatt

DEFINITION

Granuloma inguinale, as the name implies, is a granulomatous proce which usually occupies the inguinal region. It is a mildly contagious chroni and progressive autoinoculable disease involving skin and corium and occ sionally the lymphatics. The well known proclivity of the disease for the ex ternal genitalia has earned for it a place in the category of the venerea diseases. Its venereal origin, however, has never been absolutely prove (Greenblatt 1943)

ETIOLOGY

The etiologic agent of granuloma inguinale is the Donovan body o *Donovania granulomatis* (Anderson, De Monbreun and Goodpasture 1945) The disease has been reproduced in human beings by inoculation of aspirate pus from pseudobuboes of granuloma inguinale which contained no other organ isms than Donovan bodies. The Donovan bodies are strictly tissue parasites o man but have been successfully cultivated in the yolk sac of developing chicl embryos (Anderson 1943, Beveridge 1946, Dienst et al 1947), in yolk agar medium (Dienst et al 1948) and less luxuriantly in certain yolk free medi (Rake and Oskay 1948). The inoculation of this organism into volunteers how ever has not been followed by typical reproduction of the disease

INCUBATION PERIOD

Little is known about the incubation period of granuloma inguinale. The incubation period as recorded in various case reports in the literature varies from 8 days to 12 weeks. In the experimental production of the disease in human volunteers by inoculation of aspirated pus which contained only Donovan bodies the classic burgeoning granulation tissue so typical of the disease was apparent by the fiftieth day

EPIDEMIOLOGY

Granuloma inguinale is considered generally as a venereal disease and the consensus is that it is acquired by coitus. The frequency of a history of sexual exposure and the antecedent appearance of a primary penile lesion in the vast majority of males suffering from granuloma inguinale bespeaks a venereal origin for the disease. In spite of the fact that the lesions occur chiefly in the genital region some doubt exists as to its venereal origin

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HISTOPATHOLOGY

Granuloma inguinale reveals in the pure or unmixed cases a uniform histologic picture. The essential features are (1) the massiveness of the cellular reaction in which the luxuriant granulation tissue is surcharged with plasma cells, *(2) the relative and conspicuous paucity of lymphocytes*, (3) the diffuse sprinkling of polymorphonuclear leucocytes with focal collections in the superficies and papillae, (4) the pronounced marginal epithelial proliferation simulating early epitheliomatous changes, (5) the pathognomonic large mononuclear cells scattered in various numbers throughout the granulation tissue.

The pathognomonic cell is specific for granuloma inguinale. The relatively large size of the cell, the diameter of which varies from 25 to 90 microns, *and the many intracytoplasmic cysts filled with deeply stained bodies are its* cardinal features (Pund and Greenblatt, 1937).

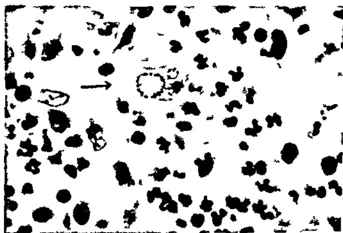


Fig. 14. Histologic section of granuloma inguinale showing pathognomonic cell. Arrow points to large mononuclear cell. (Reproduced through the courtesy of Pund, E. R. and Greenblatt, R. B., J.A.M.A. 108: 1401, 1937.)

COMPLICATIONS

Fusospirochetosis is the most common complication of granuloma inguinale. The lesions become ulcerative, progressive, foul smelling and painful and are often refractory to specific therapy. Syphilis, chancroid and lymphogranuloma venereum may be coexistent. Occasionally superimposed malignancy has been found to complicate the picture. Secondary elephantoid enlargement of the penis, scrotum or vulva and clitoris may occur.

DIAGNOSIS

The clinical picture may be so classical, the exuberant beefy red velvety tufts of granulation tissue so striking, that the diagnosis is unmistakable. Nevertheless, a diagnosis of *granuloma inguinale* should be made only when

Granuloma inguinale in this country occurs predominantly in Negroes In many instances its occurrence in white men or women definitely could be traced to sexual exposure to Negroes

CLINICAL SIGNS AND SYMPTOMS

The disease makes its appearance insidiously without premonitory symptoms or constitutional upset The disease begins as a vesicle papule or nodule The surface epithelium becomes excoriated or eroded leaving an ulcer with a beefy red granular base Early lesions have been observed to be small button like lesions raised above the surface or a fine granular film covering the glans penis with occasional nodules gently bulging the surface An early lesion which is frequently observed is a clean raised velvety smooth tuft of granulation tissue situated at the mucocutaneous border of the vaginal orifice at the preputial orifice or on the glans or inner surface of the prepuce The margin of the lesion is sharply defined The primary lesion in the female is usually found on the vulva or vagina Occasionally it is found on the cervix or in the perigenital zone The granulation tissue if traumatized bleeds easily The lesions are not painful which accounts for the fact that the patients rarely seek medical care early in the course of the disease The inguinal manifestations are secondary to the genital lesions Occasionally inguinal lesions appear without a trace of a genital lesion although a history of a previous genital lesion which healed spontaneously is frequently obtained

CLINICAL COURSE

The lesions show very little tendency to heal they spread by continuity or contiguity Extension is often slow showing only insidious progress Occasionally the spread is more rapid and there is a predilection for moist contact surfaces particularly in the crurosacral folds Daughter lesions frequently develop near the larger lesions These coalesce after a time to form extensive ulcerative processes The advancing border of the lesion has characteristic rolled edges the granulation tissue piling over onto the bordering epithelial surface

The ulcerative process may reach a stage where it remains more or less stationary for many years Secondary pseudoelephantoid enlargement of penis scrotum or labia may occur The lesions may show a tendency to scar formation at one margin and chronic progression at another Exacerbations of progression are common and sometimes so extensive as to occupy great surfaces The lesions when present for several months to years have a sour smelling peculiarly pungent characteristic odor

EXTRAGENITAL LESIONS

Most of the extragenital lesions are secondary to pudendal lesions although in a few instances purely extragenital lesions have been described Extragenital lesions occur in about 6 per cent of all cases of granuloma inguinale



PLATE IX.—Donovan bodies from spreads of lesion (granuloma inguinale).

Donovan bodies are demonstrated in spreads or when histologic study of biopsy reveals the pathognomonic cell

Spreads.—Spreads are made by obtaining a minute piece of granulation tissue *from the surface of the wound if it appears to be clean or from the* deeper part of the lesion if it appears to be markedly infected The exudate covering the infected lesions should first be removed The small piece of granulation tissue is best obtained with a sharp instrument such as a small bone curette The tissue obtained is smeared along several glass slides or crushed between two slides and then spread along the slide The slides are then dried and stained Wright stain has proved most satisfactory but Giemsa stain may be used to equal advantage The demonstration of Donovan bodies is possible in every case of granuloma inguinale



Fig 146—Donovan bodies from spreads of lesion (greatly magnified)

Biopsy.—When spreads fail to corroborate the clinical diagnosis one may resort to histologic methods Paraffin sections of biopsy material stained with hematoxylin (Delafield) and eosin or by the Dieterle silver technic will demonstrate the pathognomonic cell and the characteristic inclusion bodies with moderate ease in all cases of granuloma inguinale

TREATMENT

1 *Streptomycin*—1 Gm every 4 hours for 5 days for a total of 20 Gm is usually *sufficient to cure 90 per cent of the cases of granuloma inguinale* Complete healing usually takes place 1 to 4 weeks after cessation of therapy

Relapses will occur in 10 per cent Many of these (50 per cent) may be expected to respond to a second course of streptomycin

2 *Oral aureomycin* is a most effective antibiotic and even streptomycin *resistant cases have responded to this drug* (Greenblatt et al, 1948) The dosage is 250 mg capsules orally administered 4 *times* daily until healing is complete The usual dose required *varies from* 10 to 15 Gm Extensive cases may require *more*

3 *Chloromycetin* has been found to heal the lesions *in a* total dose ranging from 20 *to* 40 *Gm with lesions as large as* 70 *sq cm* The total dose has been *given* within an average of 12 days *Patients having had previous treatment* with other medicaments or surgery have responded to Chloromycetin In the event that examination of the tissue for Donovan bodies is still positive in a reasonable time or 5 to 7 days after Chloromycetin is started therapy should be continued until healing is complete

Greenblatt Wammock, Dienst, and West (1949) have reported excellent immediate results treating five granuloma inguinale patients with Chloromycetin These investigators have commented on advantages *in being able to give Chloromycetin orally* as *compared with streptomycin parenterally* and without appearance of nausea and vomiting even in the larger doses

4 *Antimonials*—The effectiveness of antimonial therapy decreases in direct *proportion* to the chronicity of the lesions Early granuloma inguinale responds rapidly to therapy with various antimony preparations *Tartar emetic* (1 per cent) may be given intravenously in ascending doses *beginning with* 1 c c and *increasing the dose by* 1 c c until a dose of 10 c c is reached It is administered every *2* or 3 days When the maximum is reached the dosage is decreased by 1 c c in descending strength until it is reduced to the initial dosage After a 2-week rest period, medication is again started Toxic manifestations such as joint pains, sore gums, anorexia, nausea, and vomiting are often *encountered with* tartar emetic Freshly prepared 1 per cent solutions are said to be more effective than stock ampules

Fuadin (Winthrop) *has proved to be superior to tartar emetic* It is more *convenient to administer and toxic reactions are seldom encountered* The solutions are stable and are available in 1 5, 3, and 5 c c ampules The initial dosage *of Fuadin is 1 5 or 3 c c* intramuscularly The dosage is then raised to 5 c c and given 3 times per week

Anthiomaline (Merck) is another stable and useful preparation that yields good results in a high percentage of cases It is available in 3 c c ampules and is administered intramuscularly 3 times per week Usually definite improve*ment in the lesions may be noted* within 4 to 6 weeks Either Fuadin or Anthiomaline should be continued until healing is complete Medication should then be administered at *weekly intervals for a period* of 6 months if recurrences are to be avoided If the lesions remain refractory to treatment then a change to streptomycin or aureomycin should be instituted

Donovan bodies are demonstrated in spreads or when histologic study of biopsy reveals the pathognomonic cell

Spreads—Spreads are made by obtaining a minute piece of granulation tissue from the surface of the wound, if it appears to be clean or from the deeper part of the lesion if it appears to be markedly infected The exudate covering the infected lesions should first be removed The small piece of granulation tissue is best obtained with a sharp instrument such as a small bone curette The tissue obtained is smeared along several glass slides or crushed between two slides and then spread along the slide The slides are then dried and stained Wright stain has proved most satisfactory but Giemsa stain may be used to equal advantage The demonstration of Donovan bodies is possible in every case of granuloma inguinale

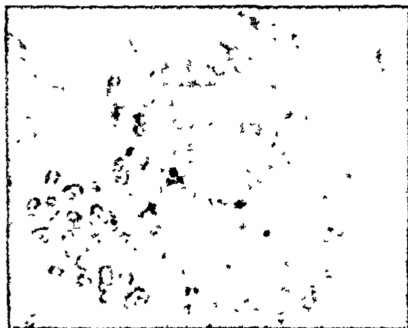


Fig 136—Donovan bodies from spreads of lesion (greatly magnified)

Biopsy—When spreads fail to corroborate the clinical diagnosis one may resort to histologic methods Paraffin sections of biopsy material stained with hematoxylin (Delafield) and eosin or by the Dieterle silver technic will demonstrate the pathognomonic cell and the characteristic inclusion bodies with moderate ease in all cases of granuloma inguinale

TREATMENT

1 *Streptomycin*—1 Gm every 6 hours for 5 days for a total of 20 Gm is usually sufficient to cure 90 per cent of the cases of granuloma inguinale Complete healing usually takes place 1 to 4 weeks after cessation of therapy

CHAPTER 24

DISEASES DUE TO BACTERIA—THEIR DISTRIBUTION AND OCCURRENCE IN THE TROPICS

OSCAR FELSENFELD

Bacterial infections usually enumerated among the tropical diseases are leprosy, cholera, shigellosis, salmonellosis, plague, tularemia, melioidosis and undulant fever. Leprosy belongs to the chronic granulomatous diseases and is caused by a Mycobacterium which, like the entire genus in which it is classified, is not strictly speaking, *a true bacterium or bacillus*. Cholera is evoked by a Vibrio, which again has a special taxonomic position. All other bacterial diseases enumerated in this group, with the exception of shigellosis, are primarily animal infections. They cause illness or carrier state in live stock, fowl, or rodents, and are transferred to man only under favorable conditions. Such circumstances arise *more frequently in the tropics*. Thus, the endemic and epidemic foci of these diseases are more frequently encountered in warm countries than in cold climates.

The principal factors which enhance the propagation of bacterial (and other) infections may be reiterated. Lack of personal cleanliness is favorable for multiplication of vermin and helps food contamination. Insufficient protection of water, milk, and food and improper preparation and lack of veterinary supervision of livestock cause the propagation of infections. Crowded and filthy housing supports the spread of disease from man to man. Where economic and social conditions and lack of education compel people to live under such circumstances, epidemics cannot be avoided. The temperature and the moisture of the tropics favor multiplication of the vectors and of the pathogenic organisms. Improper food and living habits, chronic devastating illnesses, and other factors which lower *the general resistance foster the* spread of bacterial diseases.

The absence of an adequate number of properly equipped and well staffed laboratories in numerous tropical regions, the indolence of certain governing groups, the lack of health education and mistrust toward the physician make it very *difficult in many places to draw a representative picture of the true* epidemiologic state. Many statistics are based on pure guesswork. Even such valiant attempts as that of McKinley (1935) to present the real state of affairs brought incomplete results, partly because of lack of *cooperation* and partly because data simply are not available due to the inadequate *laboratory and epidemiologic services* in several countries and colonies. During World War II the United States Army Medical Intelligence Branch collected priceless data from regions formerly closed to such investiga-

PROGNOSIS

Before the advent of streptomycin and aureomycin only 50 per cent of patients responded to therapy Recurrences in this group were quite frequent Neglected or therapy resistant patients often harbored the disease for 10 to 15 years With increasing age declining health and resistance there was a gradual activation of the lesions The ulcerations became so extensive as to occupy the whole pudendal region lower part of the abdomen buttocks and thighs The patients became anemic bedridden cachectic and finally died With streptomycin aureomycin and Chloromycetin hope may now be offered to every patient Cases resistant to streptomycin may be encountered but they are very few and these respond to aureomycin

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CHAPTER 25

BRUCELLOSIS

Maximiliano Ruiz Castañeda

Brucellosis, also known as Malta fever or undulant fever, is an *infection* of domestic animals, mainly cattle, goats, and hogs. Because of the relationship between these animals and man, this infection is readily acquired by man. In animals brucellosis is characterized by its localization in the reproductive organs resulting in abortion. Abortion can also occur in human beings but is not a necessary sequela of the infection. The disease must be considered a bacteriemia with persistence of the organisms in various organs and tissues. This results in immunologic responses which cause characteristic symptoms.

Animals while showing the common effects of epidemic abortion are infected with Brucella types which are pathogenic for the respective species. Bovines are infected by *Brucella abortus* (Bang 1897), goats by *B. melitensis* (Bruce 1887), and hogs by *Br. suis* (Traum 1914). The resemblance of these bacteria to each other was pointed out by Evans (1918). Huddleson (1934) gave definite methods for differentiating them bacteriologically.

From a biologic point of view, each species of Brucella maintains its characteristics in each respective animal but under special conditions one species of animal may become infected with bacteria originally borne by others. This is of epidemiologic importance. Bovine stock, which under natural conditions are infected with *abortus* of low virulence for man, may acquire *melitensis* which has a higher infective power for human beings. From the clinical point of view, the three Brucella strains may cause similar symptoms in spite of different virulence so that all must be considered equally harmful.

GEOGRAPHIC DISTRIBUTION

Human brucellosis occurs throughout most of the world. The prevalence of a certain variety of the infecting agent in a specific zone depends fundamentally upon the proportion of the three species of domestic animals and the food habits of the population. *In regions where the beef industry is well developed, abortus is the most prevalent* (United States, Argentina, Uruguay, Cuba, etc.). In countries where goat's milk compensates for lack of cow's milk, the infection is caused principally by *melitensis* (Mexico, the Andean zones, and perhaps in the majority of the Latin American countries). *In countries in* which pork is the predominant meat, human infection with *suis* is frequent (*certain zones* of the United States).

The proportion of animals infected with Brucella is of secondary importance for the frequency of human brucellosis. In countries where adequate precautions *are taken* in the handling and distribution of milk, infection by *abortus* is reduced to cases in *rural* zones beyond sanitary control. In tropical countries, infection by *abortus* is of little importance because, since the colonial era, it has been the custom to boil milk to prevent

tions Some of them are already available (1944) and constitute excellent contributions to our knowledge of tropical infections The Bulletin of the Office of Inter American Affairs and numerous surveys carried out by the Rockefeller Foundation and other similar institutions greatly broaden the information available in this field of medicine

Only essential improvements work and more work in the tropical field can bring liberation from bacillary (and other) scourges of mankind

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milk or a small piece of fresh cheese is sufficient to cause infection We recall a family of seven persons who acquired the infection simultaneously by eating a total of less than 100 Gm of goat cheese

PATHOLOGY

The presence of Brucellae in the cytoplasm of cells of the epithelial layer of the bovine placenta has been known since the work of Smith and Fabyan (1912) Goodpasture and Anderson (1937) and Buddingh and Womack (1941) presented important evidence in regard to the multiplication of Brucella within certain cells of the chick embryo when these organisms were inoculated on the chorioallantoic membrane An interesting finding has been reported by Meyer (1943) who found colonies of Brucella situated intracellularly in the cells of Bowman s capsule in a fatal case of *suis* infection

Nyka in our laboratory has not found intracellular Brucellae in man but his findings indicate the existence of intracellular organisms although in small numbers

It is evident that in the pathogenesis of brucellosis as suggested by Buddingh and Womack and by Meyer the intracellular position of the Brucellae plays a primary fundamental and important role in the mechanics of the infection as well as in the defensive processes a concept which must be taken into account in the diagnosis prognosis and treatment of the disease However we must not underrate the fact that Brucella can develop outside the cells especially within spaces destroyed by inflammatory processes and in fluids in various cavities

It is believed (Loeffler 1930 and most authorities) that histologic lesions found in experimentally infected guinea pigs show marked agreement with those found in man Lesions in the guinea pig were first described by Smith and Fabyan (1912) The infection produces changes similar to those of chronic lesions in tuberculosis These are observed in most organs in a perivascular or interstitial location The focal lesions consist of grouping of epithelioid cells surrounded by lymphoid cells The general aspect is that of a chronic granulomatous infection According to Hughes (1897) a large number of acute cases present no characteristic histologic lesions except in the spleen which correspond to lesions of the type observed in acute pyrexia

Sharp (1934) referred to the general appearance of the granulomatous infection and emphasized the tuberculoid form of the nodules the similarity being more marked when Langhans' cells are occasionally found but which show none of the caseation so characteristic of tubercular nodules

Meyer (1943) stated that cultures made from organs and tissues revealed considerable quantities of Brucellae especially noticeable in the kidney where the most characteristic lesions were found including the presence of Brucella colonies in the cells of Bowman s capsule This author noted massive infiltration of the stroma adjacent to the affected cells by monocytes lymphocytes plasma cells and occasionally polyblasts

spoilage In certain rural zones however milk is generally consumed fresh and raw The danger of consuming raw milk reaches incredible proportions in zones where rural populations must drink goat s milk (various regions of Northern Mexico) An important source of infection from both *abortus* and *melitensis* is cheese especially when it is freshly prepared The majority of cases observed in Mexico City are infections from eating goat cheese

TRANSMISSION

The mechanism of transmission of brucellosis to man is simple Bovine infection is readily acquired by persons who handle infected cattle through direct contact with infected membranes and perhaps by inhalation of dust

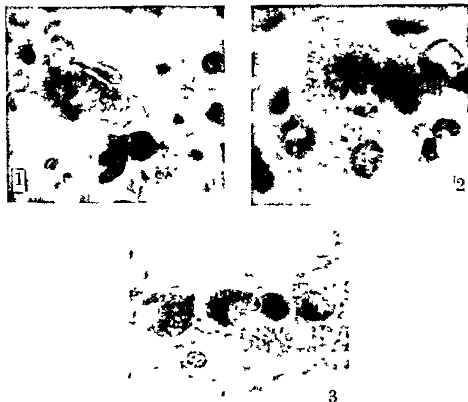


Fig 147—*1* Alveolar cell packed with *Brucella melitensis* Mouse inoculated intranasally (×1000) *2* Testis of guinea pig inoculated with *Brucella abortus* Interstitial cell (×1000) *3* Testis of guinea pig inoculated with *Brucella melitensis* Parasitized macrophages (×1000) *1* and *2* Nyka stain *3* Formalinized Clemes stain

containing Brucellae Purriel and collaborators (1944) attached special significance to these means of transmission giving them priority over infection by consumption of raw milk The most definite means of infection by *suis* is contact with *infected meat* *On the other hand a most important manner* of acquiring infection with *melitensis* is through the digestive system The virulence of this organism is such that in many cases a very small quantity of

ascertain whether that lesion was produced by Brucella or whether it w due to influences of cirrhosis of the liver from some source other than th organism

Kidney—The changes were the same as with *Br melitensis* (above)

Spleen—The spleen showed a great variety of lesions from the mos acute forms of splenitis with heavy congestion, dilatation of the sinuses swel ing of the splenocytes and a great number of polymorphonuclear leucocyte to chronic lesions characterized by a variable degree of sclerosis or by foci o necrosis with epithelioid and sometimes giant cells

Except in the liver Brucellae were regularly found in the lesions

In addition to these lesions which are considered characteristic o brucellosis many kinds of inflammatory localizations in various organs an tissues have been pointed out corresponding to the numerous complication of the disease These lesions have characteristics common to infections with out special structure varying from small cellular infiltrations to destructiv phenomena of great intensity

SYMPTOMATOLOGY

We do not wish to discuss the symptoms of brucellosis as presenting a over all picture in which the role of the specific type of Brucella has bee omitted This is often done because it is impossible to find clinical forms tha can be considered characteristic of each type of Brucella In fact the variou forms of acute brucellosis pointed out by Simpson (1940) may be caused by any of the three Brucellae This statement also applies to the insidious latent or chronic forms described by Evans (1934) as well as to the complication caused by localization of these organisms in various organs or tissues Our experience with cases principally those caused by *melitensis* has impressed upon us the necessity of considering the symptomatology as somewhat different from that described with respect to groups of patients infected by *abortus*

We wish to submit data on the incubation period of brucellosis and to present a description of the symptomatology in infection by *melitensis* as observed in over 900 patients Following this we wish to make a similar pres entation of infections by *abortus* availing ourselves of information from North and South American sources

Incubation Period—Information from various authors interested in de termining the lapse of time between exposure and appearance of the first symptoms gives an idea of the extraordinary irregularity of the incubation period There are variations which depend not only upon the type of in fective organism but also upon the virulence of each strain and the number of Brucellae which enter the body In some cases the symptoms appear a few days after exposure, in others they appear weeks months or even years later Severe infections with clinical pictures similar to influenza typhus or typhoid infections are seen when the periods of incubation are short On the other hand when symptoms appear after a long incubation period they are not striking The resulting clinical picture includes most of the chronic

Two fatal cases of acute brucellosis caused by *melitensis* studied in collaboration with Villasenor and Costero in this hospital showed but meager microscopic manifestations except in the liver, spleen and kidney, where red and white infarcts were seen with small subcapsular abscesses not larger than 2 millimeters. In one of the cases the lesions **in the kidney** were abundant, not in the glomerulus as described by Meyer but in the interstitial spaces. The inflammatory infiltrations were of variable intensity and location and contained numerous polymorphonuclear cells, lymphocytes, monocytes and polyblasts. Occasionally there were so many polymorphonuclears that an abscess-like appearance was given to the lesion. Numerous centers of infiltrated zones presented a definite necrotic aspect.

We found **in the spleen** zones of infiltration made up mainly of macrophages and lymphocytes but with numerous polymorphonuclears distributed not only in the infiltrated sites but also in a diffuse form throughout the entire organ. At several places groups of polymorphonuclears showed an abscess-like formation. Intense congestion was present, with enlargement of the sinuses and occasionally extravasation of red corpuscles.

In the liver numerous leucocytes were observed in the sinuses, as well as moderate lymphocytic infiltration in the space of Kiernan. Small lymphocytic infiltrations were found distributed throughout the organ. Small foci of necrosis and red infarcts, 2 to 3 mm., were observed. Many polymorphonuclears were seen within the infarcts. Mononuclear cells containing intraprotoplasmic formations which might have been Brucella colonies were observed in the spleen and liver.

It is of interest to add that positive cultures of various organs showed colonies from zones with microscopic lesions as well as from points where there were no lesions. The characteristic granulomatous appearance described by various authorities was not seen in these cases. On the other hand, in a chronic case of brucellosis described by Tovar (1943) and in one referred to by Costero (1945) there were found, especially in the spleen, nodular lesions made up of more or less numerous groupings of epithelioid cells surrounded by numerous lymphocytes, the general aspect of which was suggestive of tubercular nodules.

From the study of other cases, including the spleens of two splenectomized patients, Sisk found that the principal lesions are in the liver, kidney and spleen. The bone marrow was not studied.

Liver.—The liver showed interstitial hepatitis with enlarged intertrabecular spaces strewn with variable numbers of polymorphonuclear leucocytes, lymphocytes and plasma cytes. There was a marked hyperplasia of Kupffer's cells, the number was far greater than normally found. The liver cells in almost all cases showed a variable degree of fatty degeneration which usually affected the central part of the lobules. In some cases foci of necrosis were seen strewn in a random fashion all over the organ. A variable degree of cirrhosis was an almost constant feature, although it was not possible to

cases of *abortus* infection begin insidiously Chronic brucellosis sometimes called the Evans type is included in this group

Abortus infection with acute onset may be equally as severe as *melitensis* infection However in one group of cases observed in Uruguay (Purriel et al 1944) which presented clear evidence of the bovine origin of the infection the initial symptoms were not so striking While the fever was variable in form and intensity it was not sufficiently elevated so that several days or in some cases several weeks passed without any apparent need for hospitalization The clinical picture at this stage corresponds to that of influenza with marked asthenia Due to increasing general debility the patient prefers to remain immobilized When the fever is very high the physical and psychic states of the patient suggest a typhoidal condition Profuse perspiration persistent headache muscular pain usually in the flexor muscles of the legs neuralgia hyperesthesia and other nervous disturbances are concomitant symptoms Some cases show bronchial irritation and digestive disturbances accompanied by diarrhea or persistent constipation The acute phase lasts 8 to 15 days and even longer in some instances In the Purriel group of cases mentioned above improvement with complete recuperation was observed in uncomplicated cases When complications due to brucellary foci were present the clinical manifestations continued for a long time

Spink and Hall (1945) reported their observations on 35 cases which occurred in Minnesota where the infecting agent according to these authors was probably *abortus* since most of the patients had drunk milk from infected cows There were cases which began abruptly like influenza with or without gastrointestinal disturbances The fever showed a variety of forms and various degrees of intensity asthenia was marked as in the cases described by the Uruguayan authors and additional symptomatology was practically the same Other cases began insidiously In both studies in Uruguay and in Minnesota the benign tendency of the disease was marked

Although it is difficult to find many clinical descriptions of bacteriologically verified cases the impression one gathers from the literature especially the American literature is that the data presented here may be considered as the common picture of infection by *abortus*

In a comparison of descriptions of infections by *melitensis* and *abortus* it is evident that *melitensis* characteristically causes severe infections The infection begins acutely and is of longer duration than the acute phase of the infection caused by *abortus* In cases produced by *abortus* the illness frequently begins insidiously or with such minor symptoms that many cases are recognized only when they become chronic It is of interest also that in infection by *melitensis* headache is less frequent and gastrointestinal disturbances in acute cases are rare

Brucellosis Caused by Brucella Suis

This author is of the opinion in accord with reports from North American writers that the infection caused by *suis* is more severe than that caused by *abortus* and has a greater tendency to localize in the bones

brucelloses with insidious beginning. In our experience, principally with brucellosis of caprine origin, the most frequent length of the period of incubation is 2 weeks.

Following the period of incubation brucellosis may manifest itself as one of three fundamental clinical types: acute brucellosis, brucellosis with acute onset followed by a chronic phase, and chronic brucellosis with insidious beginning.

Brucellosis Caused by Brucella Melitensis

The early stage of the disease shows no difference from other acute infections, notably typhoid fever. In many cases the diagnosis is uncertain until the febrile period has extended beyond 3 weeks. During this phase many types of complications may occur. The process may vary from malignant brucellosis with a rapid and fatal termination to a benign form, at times amounting simply to an evening rise of temperature.

Fever may continue with a tendency to diminish in intensity for periods of time varying from 1 to 3 months. During this period a definite state of malnutrition becomes apparent. When the infection develops in patients under favorable conditions, symptoms are noticeably restricted; there are night sweats and pains in various joints, at times of extraordinary severity, particularly in the sacroiliac region, which necessitates immobilization because of pain. Frequently, when the patient submits to proper treatment, manifestations of the initial stage of infection gradually disappear. It is common, however, in acute cases, to find that the fever persists for 15 days to 2 months or more, followed by improvement with diminution or disappearance of the various symptoms. Improvement lasts from a few days to 2 weeks; this is followed by reappearance of fever, pains and frequently new symptoms. The fever may be continuous, intermittent, remittent or simply irregular; pains in the joints often become alarming. Among the various symptoms and complications which may arise, it is not unusual to observe orchitis, abortion, myositis, arthritis, osteitis, endocarditis and purpura. There is general debility with marked loss of weight, anemia, nervousness and mental depression, which is very characteristic. In this phase of the disease periods of relief may occur, even with disappearance of the symptoms. This fluctuation may end with marked improvement or more severe symptoms may set in, which may terminate fatally either from direct effects of the infection itself or from complications. The duration of this secondary period is variable. With the disappearance of clinical manifestations of the secondary phase the patient may become completely cured. Often, however, late manifestations appear, such as those listed, or other inflammatory changes may occur in any part of the body. The infection respects no organs or tissues.

Brucellosis Caused by Brucella Abortus

The infection appears in one of the three fundamental clinical forms indicated above. In contrast to cases of infection by *melitensis*, however, many

cases of *abortus* infection begin insidiously Chronic brucellosis sometimes called the Evans type is included in this group

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CHRONIC BRUCELLOSIS

In infection produced by *Br melitensis* or *Br abortus* a chronic phase may follow the acute stage or chronic brucellosis may appear without an apparent initial attack

Differentiation between clinical manifestations of the various forms of chronic brucellosis is difficult In general chronic cases due to *melitensis* have previously presented an acute initial stage The symptomatology of chronic brucellosis is quite variable but generally it includes the following triad a febrile condition asthenia and subjective disturbances which are seldom explained by some organic lesion To this triad may be added manifestations due to complications caused by localization of the causative agent in various organs or tissues or to secondary infections that readily occur as a result of weakening of organic defenses

The febrile cycle at times assumes a special character which justifies the name undulant fever which has been given to brucellosis The undulations are due to the fact that periods of improvement and even of suspension of the symptoms are interspersed during the course of the disease The fever curve may assume various forms It may be intermittent remittent occasionally continuous sometimes showing only an occasional rise of evening temperature Loss of weight is proportionate to the intensity of the fever as is also the asthenia and psychic condition

COMPLICATIONS

So many complications may occur during the acute phase that space forbids a complete discussion of them in this chapter We shall therefore describe only those most frequently observed in our 900 patients infected with *Br melitensis*

Four cases of abortion were observed during the phase of invasion as well as several months after this stage On the other hand 3 women with chronic brucellosis had normal deliveries

Orchitis was observed in 14 out of 265 infected males This complication appears as an intense inflammation of the testis and epididymis sometimes affecting only the epididymis The inflammation appears as a redness with distention of the scrotum swelling being unilateral or bilateral Pressure on the organ results in intense pain When orchitis occurs during the period of subsiding fever and remission of the disease there is a severe febrile exacerbation which usually lasts for several days The course of this complication is relatively rapid it generally disappears in 1 or 2 weeks and seldom leaves any evidence of pathologic changes in the affected organ

Arthritis may appear in various joints The intra articular fluid is rich in Brucella but seldom has the characteristics of a purulent discharge Joint complications generally develop rapidly followed by complete functional recovery

A relatively frequent complication in infection by *melitensis* is a painful syndrome of the gluteal region which results in functional incapacity often requiring confinement to bed for weeks and even months there are grave consequences due to physical and mental depression Since there is no evidence of important involvement of the sacroiliac joint and since the pain is generally relieved by local anesthesia it is assumed that this trouble results from local inflammatory processes in the gluteal muscles or in their sites of insertion

Nervous disturbances have been observed during the acute phase Among these are encephalitis accompanied in one case under our observation by epileptiform attacks Myelitis radiculitis and neuritis have also been re[illegible] In spite of the severity of these manifestations patients usually make a complete recovery

Osseous complications should be listed among the most important manifestations of brucellosis Spondylitis and abscesses in the ribs have been observed with relative frequency We have not encountered inter[illegible] myelitis such as Harris (1941) described

We have seen less frequently many complications due to localization of Brucellae in various organs These have been described in detail by several authors Purpura described by several authors was observed in 20 of 600 cases in which the diagnosis of brucellosis was confirmed by blood culture In some cases purpura appeared after the ingestion of drugs in other cases after administration of vaccines or filtrates of Brucella in others the purpura was thrombocytopenic In 20 patients however there was no apparent cause to justify the occurrence of such a complication In these 20 cases purpura appeared in the lower extremities It was markedly symmetrical Brucellae were isolated by scraping these lesions which had resulted from bacterial embolism distributed over a peripheral capillary with local reaction enhanced by the allergic status of the patient

DIAGNOSIS

Brucellosis shows such variations in its clinical manifestations that it is not practical to attempt to make a diagnosis without recourse to laboratory tests Clinicians have for a long time depended upon the finding of agglutinins as the fundamental element in diagnosis There has been much discussion concerning the advantages and disadvantages of this method It is inadequate to depend entirely upon agglutination without using other tests In fact there have been cases of brucellosis with bacteremia in which the agglutination test for Brucella was negative, or of slight significance In chronic brucellosis according to Evans (1938) a marked percentage of individuals show no agglutinins

Our opinion is that for practical purposes agglutination test carried [illegible] out with sensitive and specific antigens are of [illegible] nizing the existence of the infection but als[illegible] of the disease and in guiding the treatment

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Suspensions of dead Brucellae or their soluble products prepared by various technics are used as antigens Among the latter ' brucellergen prepared by Hershey and recommended by Huddleson (1934) and the extracts used by Morales Otero and Gonzalez (1938) are especially useful

Antigens prepared with whole Brucellae often cause very intense lesions at the site of the injection It is not unusual to observe inflammatory zones with necrotic centers These antigens may stimulate formation of agglutinins so diagnostic errors might be made at a later examination (Evans and collaborators 1938) For some years we have been using as a routine an extract obtained by partial trituration of a mixture of *Br melitensis Br abortus* and *Br suis* (Castañeda and Carrillo 1941) This product is diluted until definite cutaneous reactions are produced with 0 1 c c injected intracutaneously The test dose contains an insignificant quantity of antigenic material but this is insufficient to stimulate the formation of antibodies against the Brucellae

The local reaction is sufficient to be apparent even in persons of dark skin without however *producing necrotic* lesions

The cutaneous test is of great value not only for diagnostic purposes but also as a means of verifying epidemiologic data

The use of the intradermal reaction as the sole test in the diagnosis of brucellosis has been criticized and we are in accord with this point of view No test except the isolation of the organisms must by itself be considered as decisive The clinical study of a case must form the basis upon which all additional evidence in one sense or another may be built

Hematologic Studies

Our observations in a group of about 900 patients most of whom were infected by *melitensis* (Castaneda and Guerrero 1946) showed leucopenia in nearly one third and figures close to normal or above normal in the rest of the group The percentages of lymphocytes were higher than normally found with a corresponding decrease in polymorphonuclear leucocytes The increase in lymphocytes often in absolute numbers seems to indicate increased lymphogenesis in brucellosis On the other hand there seems to be an interfering effect in the yield of polymorphonuclear leucocytes which may be reduced in absolute numbers

As to the changes in morphology and other characteristics of white and red blood cells we have no data to indicate that this is of diagnostic interest in brucellosis Anemia frequently pointed out as a complication of the infection is related to the general status of the patient especially with respect to the intensity and persistence of the febrile reaction

Blood Cultures

Laboratory tests briefly indicated above constitute satisfactory proof of infection by Brucella when they are positive and in agreement with clinical data When they are negative they indicate absence of the infection But

Agglutination Test

Screening Test—The screening test is used as a preliminary test and may be performed at the patient's bedside A drop of antigen* is mixed with a smaller drop of blood taken by puncture of the finger or of the ear lobe A positive reaction shows blue clumps which separate completely from the red blood cells A negative reaction is characterized by a brownish green appearance Since the antigen is titrated to produce agglutination only when the agglutinins are at titers higher than 1 100 a positive reaction eliminates doubtful and negative tests

Negative reactions however are not considered as final until corroborated by the classical test tube reaction or by Huddleson's (1934) method

The screening test is especially valuable in rural zones where laboratory aid is not available

Titration of Agglutinins—Huddleson's rapid slide test is very useful as a diagnostic procedure and also as an indication of agglutinin content in the serum When it is desirable to determine agglutinin titers higher than 1 500 the tube agglutination method with suitable antigens is recommended

Differential Serologic Test—When a serum is positive it is our practice to use differential tests to determine the type of agglutinins present We use a substitute for the absorption method calling it the selective agglutination" method (Castañeda 1942) It is easy to demonstrate in a few minutes whether the serum is from infection by *abortus suis* or *melitensis* Identification has been completed in more than 600 cases of brucellosis where the selective agglutination test results have been checked by bacteriologic control

Opsonic Test

The opsonic test recommended by Huddleson and collaborators (1932) is an important indicator if systematically studied in each patient particularly when related to the numbers of available polymorphonuclear leucocytes It displays fluctuations often related to the condition of the patient it increases in intensity with recovery near at hand persisting after disappearance of the symptoms In order to prevent laboratory accidents by handling live Brucella we have recommended the use of formalin killed *Br abortus*

Allergic Test

This test determines hypersensitivity to Brucella or its by products It is carried out by means of intracutaneous injection of appropriate antigens In sensitive persons a cutaneous reaction occurs characterized by redness of the skin edema and painful sensation at the site of the injection Patients begin to show cutaneous reactions usually at the end of the first month of illness The reaction increases in intensity with the development of the disease often reaching a maximum months later and remains for indefinite periods

*We use an antigen suspension containing *Br abortus* and *Br melitensis* treated with 10 per cent formalin for 48 hours washed heavily tinted with methylene blue centrifuged and resuspended in 1 1 000 sodium citrate solution It is standardized with sera of known titers The concentration of the organisms is about 100 billion per cubic centimeter

drugs of uncertain or perhaps harmful effect As a consequence of this uncertain therapy the physician might be responsible for damages which could endanger his patient s life

We consider it unnecessary to recall the numerous methods and drugs recommended in the past Of those most commonly used we shall discuss briefly the treatment by vaccines which are given with the idea of increasing the immunologic defenses of the patient Experience shows the uncertainty of the results in the acute phase of brucellosis In the chronic phase it seems to us unreasonable to add to the already hyperimmune condition an increase in stimulation The administration of hyperimmune serum or whole blood has not been of value in our cases of acute or of chronic brucellosis

Chemotherapy has recently again been brought to the attention of clinicians this time based on extensive experimental work in which such drugs have shown their usefulness against Brucella Streptomycin and sulfadiazine are credited with being the most useful * Experimental work by Spink and collaborators (1948) however showed that either drug used separately has considerably less antibrucella effect if administered into infected developing chick embryos than if both drugs are administered simultaneously Application of this combined treatment to human brucellosis was made by Eisele and McCullough (1947) and by Spink et al with most encouraging results Spink et al recommended the administration of 0 5 Gm of streptomycin every 6 hours for 2 weeks and simultaneously an initial dose of 4 Gm of sulfadiazine and 1 Gm every 4 hours thereafter The sulfadiazine should be continued for longer periods This method of treatment is now on trial (1948) one must await the accumulation of sufficient data before definite conclusions can be drawn

In this respect we must keep in mind that brucellosis is often a relatively mild disease which may be of short duration with early disappearance of the infecting agent from the blood stream and that in the chronic phase of the disease the usefulness of the antibrucella agents may be of little or no value

In brucellosis one may expect that the acute phase will be followed by temporary remission and later by recurrences usually characterized by *hypersensitivity to Brucella products* For this reason we have followed for the past eight years the plan of desensitizing the patients so as to reduce to a minimum any disturbances caused principally by temperature elevations For this purpose we have used extracts obtained from Brucella very active as allergens but insufficient as stimulants for increased antibody production These extracts are the same as those used for the determination of skin sensitivity and are administered subcutaneously in 2 weekly doses beginning with 1 skin test dose and gradually increasing to 20 doses As may be expected this treatment has little or no effect on the acute phase of the disease but in most cases it may be instituted as early as possible with the hope that at the termination of the acute stage the patient may be in a better condition

*Recently aureomycin and Chloromycetin have been recommended.

judgment must be reserved until completion of those bacteriologic studies covering isolation of the organism from the blood from focal lesions or from bile urine, feces etc

Various media may be used in the isolation of Brucella from the blood but we find Bacto tryptose used in broth and agar practical * Experience has *shown the considerable difficulties in obtaining cultures from the blood of* patients and the danger of handling the material in the process of isolation and identification of Brucella In order to obviate these difficulties we have recommended (Castañeda and Guerrere 1946) the use of a double medium which has proved very valuable

Tryptose agar in amounts of 20 cc is distributed in 100 cc flat sided bottles and autoclaved The medium is allowed to solidify in one of the narrow sides of the bottle With sterile precautions 15 cc of sterile Bacto tryptose dissolved in 2 per cent sodium citrate are added The bottle is closed with an adequate rubber stopper and incubated for several days as a test for sterility Carbon dioxide may be added before or after setting the stopper

The blood is taken as usual by means of autoclaved syringes and ejected through the rubber stopper in amounts of 10 cc At 48 hour intervals the broth and blood mixture is spread over the agar layer the bottle immediately replaced in its vertical position and incubated at 36° C If the blood culture is positive colonies of Brucella may be observed in the agar layer after the fourth day but most frequently after the sixth day If no colonies are observed after 20 days of incubation the culture is considered negative

*Identification of Brucella is rapidly made by determination of the atmospheric re*quirements of the isolated organism by the production of H_2S and by the type of agglutinogen which predominates in the antigenic constituents of the organism In our laboratory we determine the type of agglutinogen by the use of selective agglutination this has given satisfactory results Recourse may be had however to the absorption of the agglutinins or to agglutination by monovalent sera recommended by Evans (1937) *and by Wilson and Miles (193- In a well equipped laboratory determination of the* type of newly isolated strains can be carried out with bacteriostatic media recommended by Huddleson (1934)

The possibility of infection by rough variants of Brucella must not be overlooked In such cases special studies too complicated to be included in this chapter may be required

Treatment

Data on the pathogenesis of brucellosis are meager yet they are worthy of consideration as a basis for treatment There can be no doubt that the possibility of development of Brucella within various types of cells—a more active development than is supposed—constitutes a serious obstacle to successful therapeutic attack Because of its intracellular position the Brucella persists in spite of the high immunity attained by the tissues This persistence explains the allergic character of the principal manifestations of brucellosis

Most methods recommended for the treatment of brucellosis are not efficacious so that we have maintained an attitude of prudent *vigilance, avail*ing ourselves of the natural defenses of the individual and avoiding using

*For use see Cradwohl Clinical Laboratory Methods and Diagnosis ed 4 vol II St Louis 1948 The C V Mosby Company pp 1478 and 1516

†Difco Laboratories Detroit Mich

depend upon widely varied circumstances. We shall give data only on one relatively frequent complication which requires special treatment.

In the gluteal region at the level of the sacroiliac joint there is often present a myalgia of such intensity as to prevent the patient from moving. The psychic effect of the myalgia is such that fear of pain on movement keeps him in bed for weeks or even months. Contractures and muscular atrophy complicate this condition. Carrillo (1944) described the technic followed in our clinic for the treatment of this complication. Five to 10 c c of procaine are injected into the painful site at a convenient depth. When the trouble is not articular the patient experiences immediate relief. When he discovers that he can move without excessive pain he acquires confidence, his appetite improves and his mental state changes. The treatment is repeated 3 to 4 times at 48 hour intervals. Usually the patient recovers his ability to move within a few days.

One of the most dangerous complications is that which results from hypersplenism leading to severe hemolytic anemia, agranulocytosis or thrombocytopenic purpura. Splenectomy may be required in such circumstances.

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to tolerate the constant discharge of products of Brucella which are accompanied by the symptoms described above

Frequently particularly when no important localizations of Brucella are present even though bacteremia continues for weeks and even months after termination of the acute phase patients submitted to the desensitization treatment present a minimum symptomatic picture Many patients have returned weeks and even months later complaining of reappearance of symptoms Renewal of desensitization improves their symptoms which gradually subside

Because of the allergic nature of most of the symptomatology in chronic brucellosis treatment by desensitization has given more consistent beneficial results On the other hand this method is of no value in anergic patients anergy frequently is found in severe and persistent bacteremia related to considerable multiplication of the organisms in the spleen liver endocardium and other important foci of Brucella

Since the treatment by desensitization causes little or no trouble to the patients it may be continued for several weeks or months As a general rule we advise continuance of treatment until the agglutination titers become lower than 1 200 checking the immunologic picture of each patient periodically

In spite of the enthusiasm over successful results by recent therapeutic methods in brucellosis we consider that the solution is far from favorable because of the complexity of the mechanism of brucellary action namely the peculiar intracellular position of the organism and the concomitant phenomena of bacterial allergy It is hoped that further knowledge of antibiotic action may help in the solution of these problems

COMPLEMENTARY THERAPY

Complications of brucellosis such as abscesses arthritis and ascites may be benefited by direct injection of sulfathiazole associated with urea Penicillin has been used successfully whenever complications due to bacterial sensitivity to that drug occur The consequences of neutropenia in brucellosis are appreciable as seen by the facility with which ordinarily insignificant local infections become severe enough to warrant surgical handling We find it necessary to extract all infected teeth remove infected tonsils and even to resort to resection of the gall bladder after confirmation of persistent infection whether brucellary or from another cause As long as a secondary abscess persists there is always the possibility that the pathogenic bacteria or saprophytes may provoke serious complications such as spondylitis myositis suppurated arthritis and osteomyelitis

In addition to changes in the white count many patients show a reduced number of red cells requiring blood transfusion in certain cases occasionally we have administered liver extract and ferrous salts to anemic patients We have administered vitamins preferably thiamin especially in cases with high and persistent fevers calcium salts have been given when needed We cannot include in this chapter those aspects of symptomatic treatment which

CHAPTER 26

TULAREMIA

LEE FOSHAY

Tularemia is an infectious disease of an extraordinarily large number of natural hosts, readily transmissible to man Although its greatest prevalence is in the North Temperate Zone, Tovar (1944) verified its existence within the tropics, and it is likely that further search will enlarge its present geographic range

CAUSATIVE AGENT

Bacterium tularense is a gram negative, nonmotile, unencapsulated, highly polymorphous microorganism with obligate requirements for cystine The morphologic units described by Hesselbrock and Foshay (1945), ranging from 3 μ to less than 0 3 micron, and comprising globi, globules, bacillary forms, delicate filaments, and minute, filtrable minimal reproductive units, were confirmed by the electron micrographic study of Eigelsbach, Chambers, and Cornell (1946), who measured minute units as small as 90 to 110 millimicrons Although it exhibits serologic relationships with Brucella, *Bact tularense* is biologically unrelated to the Brucella *or the Pasteurella, but is more closely related to certain members of the Borrelomycetaceae*

VECTORS AND NATURAL HOSTS

The chief mammalian natural hosts are rabbits and hares, all rodents, many carnivores some marsupials and insectivores, and a few artiodactyls, the rabbits and hares being the chief transmitters to man Among arthropods the chief hosts and vectors are many ticks, flies, fleas, lice, and mites, with ticks of the genus Dermacentor and flies of the genus *Chrysops being the chief vectors to man The chief avian hosts and* occasional vectors to man, are quail, pheasant, grouse, chicken hawk, and horned owl Other hosts responsible for rare infections of man, and possibly for maintenance of contamination of natural waters are certain fish, crustacea, snakes, frogs, and turtles An extensive list of *vertebrate hosts* was recently published by Burroughs, Holdenried, Longanecker, and Meyer (1945) Ticks of the genera Haemaphysalis and Dermacentor are chiefly responsible for maintenance of the reservoir of infection among vertebrates Since these ticks transmit the infection trans ovarially to succeeding generations, they are both reservoir hosts and vectors Man to man *transmission is rare Most human infections follow contact* with infected animals, principally rabbits and hares, or the bites of infected ticks or flies The proof of infectiousness of extensive natural waters by Karpoff and Antonoff (1936) in Russia, by Huseyin (1937) and Öz (1938) in Turkey, and by Jellison (1942) and Parker (1943) and *their associates* in north western United States prompts continued search for water borne infections

PATHOLOGY

The organs most frequently affected are the skin and conjunctivae regional and remotely located lymph nodes, lungs, spleen, liver, and the large serous membranes The fundamental lesion is necrosis at first coagulative, later often liquefactive The surfaces and cut sections of organs usually show few to numerous grayish white focal necroses Liquefaction necrosis

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cavities A characteristic feature is the development of a primary lesion and rapid enlargement of regional lymph nodes *without intervening lymphangitis* Regional nodes always enlarge first Further lymphatic extension may engender remote bubo formation even in contralateral nodes without corresponding primary lesions Small multiple dermal lymphangitic nodules resembling those of sporotrichosis appear on the hands and arms in about 7 per cent of cases

Fever is always present usually to 39° or 40° C (102 2° to 104° F) There is often an initial rise a remission and a secondary rise to the initial level The initial rise usually lasts from 2 to 5 days the remission from 1 to 3 days and the secondary rise from 1 to 2 weeks followed by a gradual decline to normal In the absence of regional localizations the febrile period usually lasts from 2 to 4 weeks If pneumonia is present high fever may persist for 4 to 6 weeks Fever may accompany repeated suppuration of buboes or *persisting infection in serous cavities for weeks and even for months* The fever is typically daily remittent with wide fluctuations but in the severest forms it becomes nonremittent at a high level

Cough is a frequent early symptom usually accompanied by bronchitic rales *Unless pneumonia develops it usually disappears before the third week*

Although the studies by Blackford (1935a 1935b 1941) and his associates showed that about 90 per cent of patients develop roentgenologic evidence of bronchopulmonic changes the pneumonia frequency is about 18 per cent hence the majority of early bronchopulmonic lesions do not develop into pneumonic areas Bronchopneumonia may occur in any lobe may be solitary or multiple and with or without pleurisy that may be dry or with effusion but most develop from the hilar regions By extension or confluence they may present the physical signs of lobar pneumonia Bronchopneumonia is an inconstant but an integral part of the general disease primarily hematogenous in origin Early consolidations frequently fail to produce clinical signs

The high frequency of pneumonia in the typhoidal type has suggested the possibility of a primary pneumonic type in which initial infection occurs by inhalation Stuart and Pullen s (1945) review favors this view *but the summarized evidence is unconvincing The existence of a bacteremia* during the initial phase first demonstrated by Francis (1927) has been repeatedly verified by animal inoculations and cultures of blood and indirectly by *most pathologic findings as* Foshay (1937) observed Although some laboratory workers acquired tularemic pneumonia after infected animals sneezed or coughed into their faces others who were similarly exposed and infected did not develop pneumonia The presence of *Bact tularense* in the sputum of patients with pneumonia has been confirmed frequently but not one human infection ascribable to this source has been recorded although many *hundreds of* nonimmunes have been subjected to this kind of exposure The experience of the author with a considerable number of scientific workers who were exposed to infected aerosols or dust clouds containing strains of maximal virulence was *that although a number acquired* tularemia the incidence of tularemic pneumonia was notably lower than that usually observed in the bubonic clinical

is frequent in lymph nodes The lungs may be normal or may show solitary or few large discrete nodules numerous miliary focal necroses, or solitary, multiple or confluent areas of bronchopneumonia or combinations of these lesions Pneumonias may be caused by mixed infections The heart seldom shows gross lesions Pericarditis pleuritis and peritonitis occur usually with effusion Thrombophlebitis enteritis meningitis and encephalitis have been observed also stomatitis mastitis and focal lesions in the kidneys and supra renal glands

Microscopic lesions soon exhibit subacuteness or chronicity Early lesions show chiefly necrosis of tissues and exudates often with extensive karyorrhexis older lesions become granulomatous with little or no necrosis The fundamental cellular reaction is reticuloendothelial monocyte epithelioid The exudate of uncomplicated tularemic pneumonia is typically mononuclear and may be composed entirely of macrophages The comprehensive monograph by Lillie Francis and Parker (1937) should be consulted for detailed studies

CLINICAL SYMPTOMS

The distinguishing features of the four clinical types described by Francis (1927) and the type frequencies determined by the writer for 1 443 cases are as follows

Ulceroglandular with primary lesions and regional buboes This is the commonest type with a frequency of 84 per cent

Oculoglandular with conjunctival primary lesions and regional buboes The type frequency was 4 per cent

Glandular, with buboes but without any primary lesion The type frequency was 2 per cent

Typhoidal with neither primary lesions nor buboes The type frequency was 10 per cent This type differs notably in that its pneumonia frequency is three times greater and its fatality rate is four times greater than those of the combined bubonic types

The incubation period is usually from 2 to 5 days but may vary from less than 24 hours to 13 days Prodromal symptoms are rare The onset is characteristically sudden with chills or chilly sensations fever sweats aching bodily pains and sometimes nausea and vomiting Colicky abdominal pain and diarrhea may occur at the onset Headache and mental dullness occur frequently Severe infections usually produce delirium stupor and a semi comatose state

Subsequent to the abrupt prostrating onset most patients develop chancre-like primary lesions and regional buboes Primary lesions usually develop at contaminated areas before buboes become apparent Either is usually apparent within 2 days after onset and either or both may be present at the onset Primary lesions begin as painful necrotizing papules which enlarge ulcerate and become indolent ulcers with raised edges vertical walls and ragged necrotic floors Most occur on the fingers hands or arms but they may arise on the skin elsewhere or on the mucosa of the oral, nasal, and pharyngeal

Serum Agglutination Test—The macroscopic agglutination test is the standard and preferred procedure Slide tests to demonstrate serum agglutinins may be used as presumptive tests but they are inadequate to resolve the commonest diagnostic difficulties which require estimation of titers

Serum agglutinins never appear before the eighth day of disease they usually appear during the second week and rise rapidly to high titers in the third week Infrequently their appearance may be delayed until the third week and rarely until the fourth week Third week titers are seldom below 1 640 All patients develop agglutinins unless death occurs prior to the end of the second week and even then most will reveal postmortem titers Agglutinins acquired by infection usually persist for the life of the patient the titer falling gradually Ascending titers from zero during the first week to high levels during the third or fourth weeks are wholly convincing Titers that remain at about the same moderate level in the absence of characteristic clinical findings occur typically in recovered immune individuals Ransmeier and Ewing (1941) recently presented a critique of the agglutination test

Reciprocal cross agglutination with *Brucella* may occur especially whenever the homologous titer is high Since the homologous titer is almost always the higher one cross agglutination seldom causes diagnostic difficulties This is also true for the much less frequently observed falsely positive Weil Felix reaction Since agglutinins usually persist for many years this test can never be used to indicate recovery

Intradermal Tests—Intracutaneous injection of 0 05 c c of a dilute formalin killed suspension the test dose containing about 6 000 cells provokes a specific papulo erythematous reaction after 48 hours Positive reactions occur in about 93 per cent of cases early in the disease before serum agglutinins appear Intradermal tests may stimulate agglutinin formation as noted by Friedewald and Hunt (1939) but the inconstant and low titers so produced are easily distinguishable from agglutinin curves caused by infection Immune persons usually give positive reactions for many years after recovery

Cultures—Cultures of blood or exudates on glucose or glycerol cystine blood agar are sometimes successful Isolation is more reliable after inoculation of source materials into mice or guinea pigs followed by heart blood or splenic pulp cultures at time of animal death The danger of self infection from handling infected animals is great it is less but still significant from handling virulent cultures

Smears—It is useless to attempt confirmation by examination of stained smears since it is practically impossible to distinguish bacteria from minute karyorrhectic fragments or other granules

Blood Counts—There are no characteristic blood findings Leucocytes vary from 5 000 to 20 000 per cubic millimeter with usually a polynucleosis but the counts have no diagnostic value A mild to moderate degree of secondary anemia is an inconstant finding

types Tularemia has not yet exhibited a primary pulmonic type, with air-borne transmission from person to person, analogous to the pneumonic form of plague

A variable and nonpathognomonic exanthem occurs in about 20 per cent of cases, usually during the second or third week The various eruptions are described and illustrated by Hitch and Smith (1938) Typical erythema nodosum occurs infrequently

Weakness, loss of weight, recurring chills, sweats and sensation of prostration are characteristic of the acute phase After the fourth week profound fatigue is often the outstanding complaint The gravest **prognostic sign** is the association of constant delirium or stupor with a nonremittent high fever, often but not always indicative of the onset of septicemia Additional findings confirmatory of septicemia are progressive enlargements of the liver and spleen, deepening jaundice, progressing involvements of the lungs brain, and meninges, with deepening coma

The duration of disease varies from 2 weeks to 15 months or longer, but is usually about 4 months The most frequent causes of prolonged illness are successively suppurating buboes persisting or migratory pneumonic lesions and their sequelae, and persisting infection of the pleural or peritoneal cavities Suppurative adenitis occurs in more than half of all cases with buboes, usually during the second month and thereafter Buboes that have disappeared may suddenly reappear as late as 2 or 3 years after apparently complete recovery Many of these liquefy rapidly

Cases that are mild throughout the entire course are seldom seen, but in many the symptoms that recur with the secondary rise in temperature are milder than those of the usually stormy onset These patients may be bedridden for only a few days and become ambulatory soon thereafter

The **prognosis** for survival is good in the absence of pneumonia less favorable if pneumonia is present and grave if septicemia supervenes Patients with pre-existing coronary or rheumatic heart disease are notably poor risks Most deaths occur between the eleventh and eighteenth days of disease, usually from septicemia, less frequently from severe intoxication or heart failure The case fatality rate is about 6 or 7 per cent

Relapses or recrudescences occur infrequently from 8 months to 2 years after onset Although usually solitary and of short duration, infrequent examples of repeated relapses throughout 1 to 2 years have been observed

Recovery from attack confers a permanent immunity Inapparent or subclinical tularemia is rare, and apparently limited to scientists who have either handled strains of low virulence or who have been protected by prophylactic vaccination Francis (1936) noted that repeated exposures may induce trivial local reinfections in recovered persons

LABORATORY DIAGNOSIS

Although 90 per cent of human tularemia representing the bubonic types, can usually be diagnosed from epidemiologic and clinical findings the deceptive typhoidal type often presents great difficulties Laboratory tests, if properly applied and interpreted, give extremely reliable confirmation

monary serosal or other regional localizations should be treated to avoid serious sequelae and to prevent the establishment of prolonged illness and disability

Patients who have weathered the severe phase and who have reached the fourth week of disease without pneumonia or other visceral lesions with little or no fever and without evidence of progressive bubo formation will seldom need special treatment

Ocular lesions are best treated locally with continuous wet dressings of warm magnesium sulfate saline solution with frequent lavage of the con junctival sac with warm boric acid saline solution

Primary lesions should not be incised unless secondary pyogenic infec tion requires drainage Dressings wet with saturated solution of magnesium sulfate are sufficient Suppurating buboes require drainage as soon as the nodes become liquefied

PROPHYLAXIS

Prophylactic studies by Foshay (1942) and associates indicate that prophylactic vaccination prevents many infections and markedly ameliorates the disease if it is acquired subsequently Until better vaccines become avail able personal prophylaxis must depend upon avoidance of sources of infec tion the use of rubber gloves to handle infected animals or carcasses and the removal of ticks before attachment occurs Whenever the disease is fly borne personal prophylaxis is difficult The chlorination studies of Foote (1943) and associates indicate that standard chlorination procedures should give effective community prophylaxis against water borne tularemia

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TREATMENT

General Management—Complete rest in bed is necessary during the initial phase when fever is high prostration is severe and drenching sweats are frequent Since man to man transmission is extremely rare strict isolation of the patient is unnecessary Rubber gloves should be worn to dress ulcerated primary lesions to incise and dress suppurating buboes and to perform paracenteses Otherwise there is no need for precautionary measures beyond ordinary care and cleanliness on the part of sickroom attendants

The diet should be liquid during the severe phase high in carbohydrate and fruit juices semisolid to light as the fever declines with resumption of full diet as soon as appetite returns Chair privilege and ambulatory status may be granted as soon as temperature and pulse rate are normal and as strength returns

Specific Therapy—Serum therapy according to reports by Foshay (1940 1946) induces significant lowering of mortality and highly significant reductions in morbidity Although effective in terminating prolonged illness not in excess of 10 months the most significant favorable effects follow treatment before the end of the second week of disease and especially in patients with the typhoidal clinical type

In the absence of pneumonia 30 c c of the serum administered intravenously or intramuscularly is usually sufficient If pneumonia is present the initial dose should be 60 c c and more may be necessary Reduction in fever and re establishment of mental clarity are the best guides for quantity frequency and duration of treatment

Chemotherapy—Streptomycin is a valuable and effective therapeutic agent Early reports by Foshay and Pasternack (1946) Abel (1946) Foshay (1946) and Howe Coriell Bookwalter and Ellingson (1946) indicate that it induces prompt and highly significant reductions in morbidity that it is more effective than serum therapy for the desperately ill patient but that streptomycin like serum may exert little effect in the late stages of prolonged illnesses

A total dosage of 2 Gm of streptomycin base is sufficient This may be given after solution in physiologic saline either by intramuscular injection every 3 hours or by continuous hypodermoclysis at a rate of 0 25 Gm every 12 hours for 2 days followed by 0 25 Gm daily for 4 additional days

Penicillin is ineffective* No sulfonamide nor any other drug has been *demonstrated to modify significantly the natural course of the disease*

Indications for Therapy—Early treatment during the severe initial phase will effect the greatest shortening of disease and the lowest mortality The presence of pneumonia pleurisy peritonitis or other visceral lesions are indications for prompt treatment The intervention of sustained high fever associated with delirium and stupor is an urgent indication Continued disease into or beyond the second month usually caused by lymphatic pul

*Editor's note (O F) Recently aureomycin Chloromycetin Neomycin, and terramycin have been recommended

CHAPTER 27

PLAGUE

ATILIO MACCHIAVELLO

(TRANSLATED BY ANTHONY DONOVAN)

GENERAL DESCRIPTION

Plague is an acute, febrile, transmissible disease, infectious and contagious, the specific etiologic agent of which is *Pasteurella pestis* It is essentially a zoonosis of rodents, and under certain circumstances it is transmitted to man, usually by the bites of fleas infected from rodents in the septicemic phase of acute plague The fleas abandon their natural hosts when these die of the infection, and seek blood meals on secondary hosts, one of which may be man

In exceptional circumstances, secondary pulmonary localizations may *occur in bubonic or septicemic plague, and may give rise to air borne contagion* from man to man, thus provoking cases of primary plague pneumonia without the involvement of rodents or fleas in the transmission cycle

Human plague (oriental plague, or plague "of the Orient," the "Black Death," or simply "the plague") continues to be one of the most important problems of tropical medicine On the American continent the disease manifests certain specific characteristics which will be emphasized in the course of the descriptions below

HISTORY

It is not possible to state with exactitude the first time that plague occurred among mankind although there are documents as ancient as the Bible (I Samuel, Chapters 5 and 6) wherein the disease is mentioned as "tumors in the secret parts" Dionysius the Hunchback, Dioscorides (first century A.D), Poseidonius (150 135 B C), Rufus of Ephesus (*circa* 100 A D), and Oribase (325 400 A D) among others, described or cited data referring to plague, especially in Libya Egypt, and Syria The epidemics known as the plague of Athens, described by Thucydides (430 B C), the Antonine plague, and the plague of Carthage all antedating the Christian era, possibly were not plague However, the great pandemic which began in 542 A D , generally called the plague of Justinian—*glandularia* or *pestis inguinaria*—was undoubtedly plague, [illegible] Italy, Gaul, Germany, and has been descrit [illegible] s of Caesarea in Constantinople, and by [illegible] mic manifestations it receded from Europe and Asia Minor, having wiped out half the population of the Roman Empire

In the fourteenth century, from 1346 to 1353, there occurred the most terrible of all pandemics of plague Beginning in Asia Minor it advanced to eastern Europe where it took a toll of 13 million victims (Hecker, 1832) It then extended along the Mediterranean Sea, and progressively invaded all the countries of Europe except *the arctic zones* of Greenland and Iceland, with death of a quarter of the population of the continent Pope

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Indies, East Africa, Madagascar, West Africa, and in South America, Brazil, Bolivia Peru, and Ecuador, sylvatic—United States, principally the western states, China, Mongolia Transcaucasia, South Africa, and Argentina

ETIOLOGIC AGENT

Pasteurella pestis, discovered by Yersin in 1894, is a member of the group causing hemorrhagic septicemias Taxonomically it belongs to the genus Pasteurella, and may be characterized as a heterotrophic microorganism, 1 to 2 microns long a coccobacillus but with accentuated pleomorphism, nonmotile, nonspore forming, rarely capsulated, often showing a pseudo capsule or envelope (Rowland, 1914), aerobic and a facultative anaerobe, easily stained with the aniline dyes, with a characteristic bipolar staining gram negative Under favorable conditions the morphology is variable, giving rise to the so called involution forms It grows easily on ordinary media It does not liquefy gelatin broth is

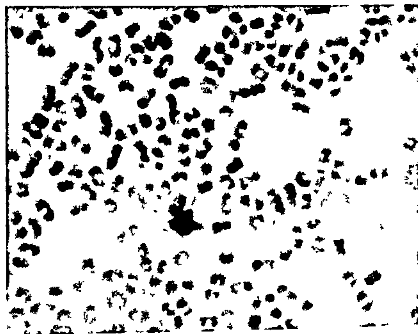


Fig 148—*Pasteurella pestis* (×3 000 approx)

not made turbid, but a film is formed, with stalactite formations (Haffkine), which break on the slightest movement Milk is not coagulated, nor is litmus milk altered or at the most a slight acidity develops On solid media the colonies appear like dewdrops in 48 hours, and soon form a basal extension on which secondary colonies grow Usually only rough colonies are described whether virulent or not, but some authors also describe smooth colonies (Pirie, 1927, Rachinski, 1930, Otten, 1934, Pokrovskaya 1934, Macchiavello, 1941) Excessive envelope formation causes a viscous growth Indol and H_2S formation, and Voges Proskauer test are negative Rhamnose and glycerine are occasionally fermented, the latter only by certain strains called "glycerine postive" or "alpha" by Kurauchi (1930), and "continental" by Berlin and Borzenkov (1940), in contrast with the other "glycerine negative" "beta," or "oceanic" strains Optimum temperature is between 25° and 30° C Growth takes place between 0° and 43° C.

Past pestis constitutes a single serologic group Different strains vary in virulence, morphology, colony structure etc It has slight resistance to the effects of external

Clement VI estimated the total number of deaths caused by the Black Death to have been 42,836,486 Pneumonic plague was mentioned for the first time (Guy de Chauliac, 1363, and others), as well as quarantine measures which were initiated in Reggio, in 1374, and in Venice, in 1422, and were adopted by other countries

Between the fifteenth and eighteenth centuries epidemic outbreaks of plague continued, notably those of Milan, 1630, London, 1665, in which year 60,000 of the 450,000 inhabitants of the English capital died of the disease, Marseilles, 1720, where the epidemic was so intense as to cause a thousand deaths daily, and a total of 40,000, Messina, 1743, where 43 000 perished, and Russia, 1770, with a mortality of 80,000 In the nineteenth century, plague retreated toward the Orient, and in passing caused the epidemics of Constantinople in 1803 and 1813, with final outbreaks in Benghazi, Tripoli, in 1858, and in Russia, 1878 1879

The disease was now thought to have been dislodged definitely from Europe when in 1894, the city of Canton was invaded by the infection from Chinese Yunnan In 1896 plague appeared in Bombay, transported from Hong Kong or Pakhoi, or, according to Hirsch directly from Guhrwal and Kumaun Rapidly the epidemic extended to various points in India* by land and water routes, and soon to the entire world, obtaining a foothold in South America in 1899, and in North America one year later

Curiously enough, plague entered South America by the inland river port of Asuncion, Paraguay, in April, 1899 (Agote and Medina, 1901) From here the infection was transmitted to the Argentine ports of Rosario, Formosa, Corrientes, and Buenos Aires (September, 1899, to January, 1900) The second incursion of plague on the continent was at Santos, Brazil, in 1899 (Andrade, 1899) and the third at Montevideo, Uruguay, in 1900 (Fernandez Espiro, 1916)

On the west coast of South America, plague first occurred in 1903, at Callao, Peru (Artola 1903) and soon after in Iquique, Chile (Macchiavello 1932) In 1904, Antofagasta, Chile was infected directly from India by means of a shipment of jute sacks (Ferrer, 1905) In 1908 the chief plague episode in South America began in Guayaquil, Ecuador (Suárez, 1927) From there the infection jumped to LaGuayra, Venezuela (Acosta and Razetti, 1909) Bolivia was infected much later in 1921 1922 but the source of the infection is not clear (Veintemillas 1936)

In the United States the disease was reported in San Francisco on March 6, 1900 (Kinyoun, 1901) Soon murine plague spread inland and gave rise to the disease in wild rodents, and this type of infection, suspected by Blue in 1903 and confirmed by Wherry (1908), has been maintained and has been spreading eastward up to the present time

Cases of plague were reported from Mexico, in 1902, at Ensenada de Todos los Santos and Mazatlán (Liceága 1903) With the exception of Haiti, Colombia, and Central America (but including British Honduras and Panama), all of the countries of the American continent have suffered plague infection to a greater or lesser extent (Moll and O'Leary, 1940 1942)

GEOGRAPHIC DISTRIBUTION

Nearly every important country of the world was invaded during the course of the last pandemic which originated in Yunnan, China At present the principal endemic foci of plague in rodents are murine—India, China, Manchuria, Mongolia, Burma, Dutch East

*It was during this epidemic that the most notable contributions to the knowledge of plague were made by Kitasato (1894) Yersin (1894) Hankin and Leumann (1897), Childe

rat burrows Physical conditions favorable to plague may be nautical (ports) urban rural or sylvatic the first three with relation to domestic rats the rural conditions with relation to wild rodents which although living separate from human habitations share with rural man the areas cultivated by him or his agricultural or field dwelling neighbors the sylvatic totally independent of man this explaining the rarity of human plague of sylvatic origin

Social conditions influence the development of plague through population density congestion and use of buildings the facilities existing for the renewal maintenance and increase in rodent populations etc



Fig 149 —*Xenopsylla cheopis* in act of copulation

External climatic conditions the *macroclimate* define the geographic limits of plague principally through the effects of humidity and temperature on fleas The incidence of the disease is also influenced by the mechanical action of torrential rains on rats and fleas when they are dislodged from burrows (Eskey 1934) Climate also influences incidence of this disease through the effects of cold and possibly through atmospheric oxygen tension by effecting the development of the pneumonic forms Temperature and humidity govern the developmental cycle of the flea including procreation evolution from egg to adult and longevity they affect the relationship between fleas and hosts the periodicity and frequency of the infection the duration of extrinsic incubation the duration of the proventricular blockage in plague infected fleas the hibernation of fleas and their survival time away from their hosts they influence moreover the initiation duration and decline of the so called plague seasons " which vary from one locality to

agents such as sunlight and desiccation except when protected by organic substances It deteriorates rapidly under tropical conditions (Macchiavello and Paracompos 1941), it maintains its viability and virulence in the cold (Kasanski 1898 Francis 1943) Experimentally it produces typical disease in laboratory rodents differentiation is aided by its property of penetrating intact or slightly abraded skin and mucous membranes (Albrecht and Ghon 1898 1900)

EPIDEMIOLOGY

Apart from the etiologic agent the epidemiology of plague is influenced by the hosts and vectors of the infection by the surrounding conditions and by the sources and means of contagion and spread of the disease

Hosts

Plague is primarily a disease of rodents these rodents acting as hosts Taxonomically they belong to the families Muridae (rats and mice) Sciuridae (squirrels and marmots) Leporidae (hares and rabbits) Jaculidae (gerbilles) and Cavididae (guinea pigs) Ecologically rodents may be classified as domestic especially those of the subfamily Murinae genus Mus and Rattus wild those most closely related to plague being Sciuridae of the genera Citellus and Marmota and hibernating rodents the more important of these being the tarabagan (*Arctomys bobac*) of Mongolia and Transbaikalia the suslik (*Citellus citellus*) of Russia the gerbille (*Taterona lobengulae*) of South Africa and the ground squirrel (*Citellus beecheyi*) of the United States In Asia the Sciuridae are the ancestral reservoirs of plague in Africa and America these have been infected by domestic rodents Among the latter those most actively involved in plague are rats especially *Rattus norvegicus (Mus decumanus) Rattus rattus rattus* and *R r alexandrinus* which are differentiated by their habits (sewer rats roof rats and palm rats respectively) and appearance Plague is infrequent in animals other than rodents There is mention of its occurrence in monkeys Insectivora Carnivora (especially cats ferrets and the mongoose), in camels d delphis etc

Vectors

The principal vector of plague infection and practically the only one is the flea (Ogata 1897 Simond 1898 Gauthier and Raybaud 1903) an arthropod of the class Insecta order Siphonaptera the principal ones being Pulicidae subfamily Pulicinae with the genera Ctenocephalides Hoplopsyllus Juxtapulex Pulex and Xenopsylla (fleas of the dog and cat of squirrels of pigs of man and of rats respectively) Dolichopsyllidae subfamilies Ctenophthalminae (genus Ctenophthalmus) and Dolichopsyllinae (genera Ceratophyllus Diamanus Nosopsyllus Oropsylla Orchopeas Opisodasys Opisocrostis, and Thrassis) the genus Nosopsyllus (*fasciatus londiniensis* etc) being fleas of rats in cold or temperate climates and the others principally infesting sylvatic rodents marmots squirrels and others Malacopsyllidae of the genus Rhopallopsyllus which includes the fleas of domestic and wild guinea pigs Tungidae principally the genus *Echidnophaga (E gallinacea the chicken flea)* and *Hystrichopsyllidae among which the* Leptopsyllinae *L musculi (segnis)* the domestic mouse flea is of interest to us Besides the fleas of wild rodents the fleas which are important in the transmission of plague are the Nosopsylla in temperate climates and in hot climates the Xenopsylla especially *X cheopis* and secondarily *X astia* and *X brasiliensis*

Ecologic Conditions

Ecology plays a preponderating role in the development maintenance extension and decline of plague with regard to surrounding physical conditions social conditions the external macroclimate or the microclimate of the

duced by the bite Climatic conditions which regulate pulicine biology are important in defining the plague season Carrying over of the infection from one plague season to another depends largely upon whether the epidemic is complete or incomplete (Gill, 1928, Browning Smith 1912, Kunhardt, 1912, Strickland 1933), for repetition of the disease is more apt to occur when a number of susceptible rats have survived among the murine population

A plague epizootic in a locality may not be accompanied by epidemic manifestations but these generally occur in variable grades depending largely upon the species of rats and fleas present When *R norvegicus* co exists with *R rattus* there is first an epizootic among the Norwegian rats, then among the latter rodents and, later, human infection (Indian Plague Research Commission) In hot, tropical climates and in cold climates an epizootic may remain completely subterranean, without producing a single human case, the epizootic being favored by the favorable microclimate of the nests

When an epizootic is complete, that is to say when it affects all the rodents of a locality, it tends to disappear in a single plague season When it is incomplete, it tends to perpetuate itself year after year Perhaps the role of the fleas is important in maintaining interseasonal plague in certain countries as has already been stated

Rats play an important role in the transportation of plague to distant parts ("metastasis"), but perhaps fleas are even more important than rats In the Western Hemisphere, infection along the coast of the South Pacific (Chile and Peru) was transmitted through bales of jute bags from India carrying infected fleas This was suspected by Long and Mostajo 1934 and proved by Macchiavello 1945 Human epidemics are conditioned entirely by the variables rats, fleas, and climate, to which must be added the degree of contact which rats have with men and the density of the human population From the practical point of view every human case of plague should be considered as terminal except cases of plague pneumonia The intervention of *Pulex irritans* in the transmission of plague from man to man appears unimportant (Petrie and Todd, 1923, Martin, 1913 Macchiavello, 1944), although a few authors consider it relatively important (Wilkinson, 1920, Lethem, 1923, Hirst, 1922, Wu Lien teh, 1926, Eskey, 1930)

Transmission of plague pneumonia occurs by droplet infection as in other respiratory infections Pollitzer (1943) has suggested that the decline in epidemics of primary plague pneumonia is due to the fact that the infection is so grave and the secondary septicemia develops so early that the patients die before they begin to cough and expectorate, thus cutting the chain of contagion

Sylvatic plague is maintained principally by the involvement of its own vectors, which act in part as reservoirs On the other hand the role played by these same animals in maintaining the latent infection during hibernation is also important In Asia and Russia human infection from wild rodents in most cases takes place by direct contact

In only three American countries—the United States Argentina, and Brazil—is there evidence of the extension of plague from domestic to wild rodents, but the definite and independent establishment of the infection in wild rodents has been proved only in the United States The actual situation with regard to sylvatic plague in North America has been reviewed by Meyer (1942) In 1903, Blue suspected the relationship between a fatal case of plague occurring in Contra Costa County, California and squirrels which had died in large numbers between 1903 and 1905, by a plague epizootic proved by Long and Wherry By catching and exterminating squirrels, which was begun by Long Wherry (1908) was able to prove plague infection among them In 1910, under the direction of

another Different species of fleas require different levels of humidity and temperature to transmit plague *X cheopis*, for example transmits the infection most effectively at temperatures between 15° and 26° C, with humidity from 75 to 95 per cent *Nasopsyllus fasciatus* and *N londiniensis* can transmit at lower temperatures, but with decreased activity (Raybaud, 1911, Bacot, 1915, Macchiavello, 1942)

Microclimate refers to the conditions within the rat burrows, which may differ greatly from those of the external air The progressive occurrence among rodents of the completely subterranean and "silent" epizootics is made possible by the influence of the microclimate (Buxton, 1933 Russell 1934 Macchiavello 1941) It also favors the survival of plague infected fleas in rat burrows for long periods of time—up to 8 months for *X cheopis*, according to observations of the author in Peru (1945)

Epidemiologic Mechanism

The sources of plague infection are the blood of infected rodents in the septicemic phase of the disease and the sputum of human plague pneumonia cases, the route of transmission is the pulicine vector or air borne droplets Other materials of human or animal origin also may be infectious—urine, feces, the skins of wild rodents—but this is exceptional Regarding the dissemination of plague, it has been observed that the great pandemics originate in the ancestral foci of the disease whereas epidemics within a country after the first invasion, originate from other more or less recent outbreaks and locally there is generally an annual recurrence *in situ*

It is not known what was the mechanism of plague infection before the Norwegian rat (*R norvegicus*) which reached Europe in 1716 (Jorge 1928), and the black rat (*R rattus*) (invading that continent with the return of the Crusaders in the twelfth century) had attained the preponderance of today (Hinton, 1918)

The role played by rats in the epidemiology of plague is influenced by several factors, such as the period of procreation the density of the murine population the development of immunity or resistance etc, but maintenance of plague by chronic infection, by cannibalism among the rats or by other means is unimportant A better explanation for the perpetuation of the infection is the continuous passage of plague from rat to rat, in violent outbreaks in months climatically favorable for plague (plague season), and in a more attenuated form during the remainder of the year (Russell, 1934) This explanation however is not completely satisfactory nor has it been proved There is an increasing tendency to attribute to fleas the preponderating role in the maintenance of interseasonal plague (Evseeva and Tirsov 1932, Wassilieff, 1933, George and Webster, 1934, Macchiavello, 1945) just as earlier the importance of the flea in the transmission of the disease was proved

Plague of fleas is not always transmissible Blockage of the proventriculus by a plug of *Past pestis* is necessary before the flea can transmit the disease Blockage occurs only after a period of extrinsic incubation of the infection, which is shorter in the *X cheopis*, longer with *N fasciatus*, and also varies with climatic conditions (Bacot and Martin 1914, Eskey and Haas, 1940) A "blocked" flea infects the blood which it has ingested from a healthy individual, in its buccal cavity The blood is regurgitated and thus infects the wound pro-

PATHOLOGY

In laboratory animals the principal signs of experimental plague are necrosis at the point of inoculation; neighboring lymphadenopathy; gelatinous edema and congestion of the subcutaneous tissues, especially around the aforementioned gland enlargement, showing an intense periadenitis; congestion, hemorrhage, or caseation of the gland, necrotic points in the spleen or liver accompanied by hypertrophy and cloudy swelling; rarely necrotic points or areas in the lung; pleural effusion; hypertrophy of the heart, congestion, emboli, or hemorrhages in the serosa, septicemia. In many animals the localization of the buboes in spontaneous plague is different from that in experimental plague, and is due to the site of predilection of the fleas (the neck in



Fig 150—Typical plague lesions of lymph glands and spleen in guinea pig inoculated by abdominal scarification Note also lung lesions, which are seen less frequently

rats) Both chronic plague and the "inapparent" plague mentioned by McCoy (1910), Morales (1921), Bordas et al (1922), Williams and Kemmerer (1923), Long (1932), and Macchiavello (1932) have been found by us in South America, although we are not prepared to define their epidemiologic importance The type called "peste mitigada" by Swellengrebel and Otten (1914) is seen more frequently; this is very similar to that found in rats in certain zones in Peru We have described a special pathology in laboratory animals inoculated with Brazilian strains of *ingua de frio* (ambulatory plague) (1941).

McCoy, plague had been found in 402 of 150 000 squirrels examined (0 26 per cent) Studies by this author and by Meyer and Eddie proved the susceptibility to plague of a series of wild rodents which later were found infected in nature Until 1934 the California ground squirrel *(Citellus beecheyi beecheyi)* was the only rodent recognized as responsible for sylvatic plague By 1942 Meyer and Eskey had extended the list to 31 rodents as follows *Citellus beecheyi douglasii C b fisheri C armatus C beldingi oregonus C columbianus columbianus C c ruficandus C lateralis chrysodeirus C richardsonii elegans C r nevadensis C r richardsonii C variegatus grammurus C v utah C washingtoni loringi C w washingtoni* all of these corresponding to six large and nine small species of ground squirrel red squirrels of the genus Tamiasciurus *T douglasii albolimbatus* flying squirrels of the genus Glaucomys *G sabrinus lascivus* chipmunks of the genus Eutamias *E leucurus cinereus E panamintinus* and the marmots *M flaviventris engelhardti* and *M f nosophora* Together with these Sciuridae the family Cricetidae of native wood rats and wood mice is represented by the genus Neotoma *(N cinerea occidentalis N fuscipes mohavensis N lepida intermedia)* and by the genus Peromyscus *(P truei gilberti P truei truei)* and the family Heteromyidae by the genus Dipodomys *(D ordii ordii* the kangaroo rat The order Lagomorpha (rabbits and hares) is represented by *Sylvilagus nuttallii nuttallii*

By inoculation with an emulsion of fleas obtained from rodents Eskey was able to establish the experimental transmitting capacity of about twenty of the fifty species found on sylvatic rodents Although it is known that *D montanus* and *H anomalus* parasites of *C beecheyi* are capable of transmitting plague very little is known of their bionomics

In 1941 plague infection was known in 12 of the western states of the United States and in the Province of Alberta Canada Of the 504 cases of human plague which occurred in the United States between 1900 and 1944 only about 65 were related to sylvatic plague, nearly all of these in California The true causes of the extension of sylvatic plague into new areas are difficult to determine Infection by contiguity plays a certain role and possibly also the transportation of infected fleas by field mice or by certain predatory birds (Jellison 1939) which are resistant to the disease

In Argentina human plague of sylvatic origin is also rare and it is possible that originally sylvatic or field rodents contracted plague from domestic species Uriarte (1935 1936) Savino (1935) De la Barrera (1936 1939 1940 1942) Pardal (1941) Alvarado (1938) Falla (1941) and others have studied the epidemiology of sylvatic plague calling it at times rural or field plague According to these studies rodents found infected up to the present time are *Graomys griseoflavus griseoflavus Gr gr centralis Hesperomys murillus cordobensis Galea musteloides leucoblephara Microcavia australis M a joannia Lepus europeaus* etc A recent paper of Savino (1944) suggests nevertheless, the concomitance of plague in rats with epizootics in rodents termed peri domestic Further studies are required to establish the independence of sylvatic plague as a primary entity Studies are also lacking on the vector capacity of a large number of new species of fleas collected by De la Barrera and classified by Jordan (1939 and 1942) such as *Hectopsylla gemina H cypha Polygenis platensis cisandinus Tanallus galeanus Dysmicus barrerai D hapalus D ivanus Tiarapsylla argentina T amastus plesius T longinasus Dolostichus octomyos Craneopsylla andricus Ectinorus trionyx E disjugis E polymerus E setosicornis* etc Experimentally sensitivity to plague infection has been proved in a large number of wild rodents although these have not been found spontaneously infected

The author (1941) demonstrated that true sylvatic plague does not exist in Brazil Epizootics which at times are extensive among sylvatic rodents *Galea spixi* rabbits etc, accompany the infection in field rats *Cercomys Oryzomys intermedius* and mice The species *Peramys domesticus* and some *Didelphis* species appear to act as intermediaries between domestic and sylvatic plague episodes The climatic conditions in open fields especially the extreme dryness of the air impede the maintenance of a pulicine fauna in sylvatic animals *X cheopis* in the few months of the year in which the climate is favorable is a temporary parasite of sylvatic rodents being transported by *Galea* and the other animals already mentioned Sylvatic plague has not been described in the other South American countries

the designation *primary* and the later additional clinical pictures as *secondary*—definitions justified by their physiopathologic evolution

Although cutaneous plague and gastrointestinal plague may on occasion appear initially as primary clinical forms intrinsically they are variations of the bubonic or septicemic types The so called cerebral plague plague meningitis chronic plague plague marasmus *pestis minor*, or *minior*, ambulatory plague and *pestis major* should not be considered as independent clinical entities

PRIMARY BUBONIC PLAGUE

Period of Incubation

The period of incubation is from two to five days with a maximum of ten to twelve days In cases of accidental inoculation (Pestana and Levi in Oporto Strickner in Bombay Evans in Calcutta) the period was from two to three days In 26 cases which had had only one exposure to infection the author found an average incubation period of three and a quarter days including the time the flea delayed in biting the individual In India incubation periods of twelve to fifteen hours have been reported

Prodromal Symptoms

In the great majority of cases the disease has an acute onset without premonitory symptoms In cases where the invasion is slow it is difficult to define which symptoms should be catalogued as prodromal especially if the cardinal sign—the bubo—appears late If the chill is considered as the initial symptom the *prodromal symptoms* may on occasion include general weakness anorexia dizziness nausea lumbar pain restlessness and weakness of the extremities The primary cutaneous lesions are at times of great importance

Invasion

Most commonly the invasive period is not only sudden but extremely acute the disease beginning with a single prolonged intense chill or with less severe but repeated chills accompanied by trembling or shaking The initial clinical picture resembles that of any grave infectious disease After the chill there follow fever weakness headache nausea vomiting anxiety retrosternal constriction vague aches backache conjunctival injection vertigo a reeling gait (plague drunkenness) swollen facies furred tongue rapid pulse dyspnea etc At times in a few hours and usually within a day the disease is fully developed

Course

During this period one or more of the following symptoms and physical signs are seen varying in intensity from the complete absence of one or more to the predominance of a group giving a special clinical picture The clinical manifestations vary from one epidemic to another or in the same outbreak and even in the same house the cases are subject to great individual variation The nervous digestive respiratory and lymphatic signs and symptoms are

In human plague the pathologic findings may be summarized as follows

In bubonic plague (1) A vesicle indicating the site of the infective bites is rarely observed (2) congestion hemorrhage and edema of the lymphatic glands especially those which make up the primary bubo surrounded by edema and periglandular infiltration and by a hemorrhagic exudate due to extravasation of blood (3) toxic destruction of the vascular and lymphatic endothelium manifested by blood extravasations and by cutaneous and serosal petechiae (4) congestion of all the organs especially the spleen liver brain meninges and kidneys (5) dilatation of the right heart with fatty degeneration of the cardiac muscle (6) hypertrophy of the spleen

In secondary plague pneumonia the lymphatics of the parenchyma are especially involved while in primary plague pneumonia the process is essentially an alveolitis (Nattan Larrier and Richard 1931) At first the pneumonia is lobular later there is a tendency to lobal involvement There are congestions of the bronchial mucosa and hypertrophy of the bronchial glands there is also congestion of the larynx and trachea An exudate which is hemorrhagic but which contains little fibrin fills the alveoli and bronchioles desquamated cells and enormous numbers of *Past pestis* are found in this exudate In the septicemic form pathologic findings are relatively lacking except for generalized congestion and splenic hypertrophy

A detailed study of the physiopathology of experimental plague infection was made by Macchiavello and Uriguen (1944) in guinea pigs using Ecuadorian strains characterized by their great invasive capacity and slight toxicity These studies may help in understanding the mechanism of the secondary pneumonic localization in bubonic plague Primary plague pneumonia has been intensively studied by Wu Lien teh (1926 1936)

CLINICAL PICTURE

Clinically there are two types of human plague with and without buboes The latter may occur with septicemia or with pulmonary localizations It is for this reason that three clinical forms of plague are usually described bubonic septicemic and pneumonic

The relative frequency of the bubonic type predominates but is variable from one place to another In India 70 per cent of the cases are bubonic and the rest septicemic pneumonic plague being rare In Chile in 1903 of 214 human cases of plague the frequency of type was bubonic 70 6 per cent ambulatory 9 5 per cent septicemic 15 5 per cent pneumonic 4 4 per cent In Brazil in 1939 1940 of 205 cases the proportions for the same types were 71 2 per cent 19 per cent 9 8 per cent and 0 0 per cent In Ecuador Saenz Vera (1939) found that whereas on the coast only 0 5 per cent were pneumonic cases in the sierra there were approximately 25 per cent

Bearing in mind that each one of these clinical forms may develop into the other types it is convenient to define the original clinical pictures with

development of fever and at times preceding it there occurs an intense frontal headache at times almost unbearable and resembling migraine

Nausea, followed by vomiting at first mucous later bilious is an early symptom this may disappear or persist throughout the course of the sickness Essentially it is of nervous origin exceptionally only is it due to gastro intestinal causes The same is possibly true with the **diarrhea** and **constipation** The diarrhea is fetid at times dysenteric and at times choleriform the latter is more frequent in the septicemic cases The **tongue** shows a creamy or whitish central coating with the tip and borders clean and red The coating is dry with a mother of pearl or porcelain like luster which finally becomes *coffee colored or yellowish ("sulfur tongue")* and at times even almost black The lips gums and teeth are covered with sordes The tremulous tongue is protruded with difficulty Symptoms real or apparent and signs related to the digestive apparatus are anorexia or a voracious appetite thirst which is often very intense injection of the fauces pharynx and palate inflamed tonsils covered with a membrane dryness and burning of the throat a fetid yellowish diarrhea

Respiratory symptoms usually are not notable except in those grave cases in which a developing pulmonary edema causes a marked dyspnea with as high as 30 to 50 respirations per minute The patient constantly complains of thoracic oppression and constriction especially retrosternal pain Cough appears late and produces only slight sputum which is at first viscous and later purulent but without blood which is almost always present in pneumonic cases *Physical examination of the lungs shows congestion* and bronchitis Late in the course of bubonic plague especially in the less acute cases a secondary pneumonia may develop recognizable by the accentuation of the described symptoms by diminution of vesicular breath sounds by crepitus and by aggravation of the general condition These secondary pulmonary localizations are not as serious as primary plague pneumonia and many of the patients recover However this is very important in the genesis of epidemics of plague pneumonia

In the **cardiovascular system** the alterations are not intense at the beginning and may even be entirely absent in benign cases In toxic patients there are precordial oppression and *tachycardia of from 110 to 140* per minute not always in relation to the degree of fever and the fall in arterial blood pressure The initial tense pulse soon becomes weaker and more frequent then dicrotic then anacrotic with disappearance of the rebound wave and finally thready intermittent and so imperceptible that it cannot be counted Sudden death due to cardiac failure may occur at any moment in the course of the disease and sometimes during convalescence Cardiac sounds are weak but otherwise normal The septicemia may be detected *in the blood* even in benign cases and before the appearance of fever A polymorphonuclear leucocytosis with neutrophiles predominating is the general rule

***Nervous system** symptoms are very important* as they give an indication of the apparent severity of the cases although those with the most marked

those which contribute most in defining the general aspect and the apparent or real gravity of the cases The **fever** develops sharply the body temperature *rising to 40° to 41° C (104° to 105.8° F) and sometimes higher* The maximum temperature is usually not reached during the first 24 hours but in the afternoon of the *second or third day* *The fever may run an irregular* course, but usually there are daily morning remissions Between the third and fifth days there may be a considerable drop in temperature, as much as two or three degrees centigrade (Valassopoulo 1901, Simpson, 1905) followed by a secondary rise which may reach or pass the previous level with a renewed intensity of the symptoms In one or two days more the fever again

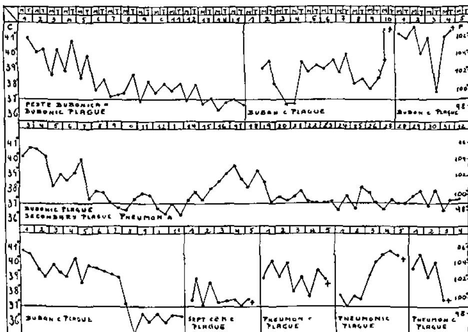


Fig 151 —Temperature curves in bubonic plague secondary plague pneumonia septicemic plague and pneumonic plague

diminishes and morning remissions occur These are each time more accentuated, with the afternoon rise in temperature less every day until in five to eight days a normal temperature is reached or there continues only a slight hyperthermia In some cases the temperature remains above normal for ten or more days Late temperature rises are usually due to complications

The **temperature curve** is not of great prognostic value although fever is higher in serious cases A sharp fall in temperature with increase in pulse rate is a bad prognostic sign and when due to collapse, results in a rapidly fatal termination A gradual decline in temperature is a sign of a normal course Toxic cases may show hypothermia In benign cases there might be no elevation in temperature during the entire course With the



Fig. 152—Primary cutaneous plague lesion (plague carbuncle)



Fig. 153—Primary plague carbuncle overlying submandibular bubo

nervous signs are not always necessarily fatal Symptoms of nervous system involvement are rarely lacking in serious cases but they may be insignificant with relation to the gravity of the lymphatic signs they vary from one case to another and during the course of the disease some being transitory and others continuous

In the beginning there are depression vomiting nausea headache a staggering gait difficulty of speech with stuttering insomnia restlessness and at times a tendency to wander even from one town to another Later motor and sensory involvement is the rule although this is not always grave The general aspect of the patients depends in large measure upon the degree of nervous involvement At times they appear semiconscious and mentally con fused answering questions with difficulty with slow hesitant speech leaving words and phrases unfinished and with stuttering The mental confusion may progress to complete cloudiness hebetude and stupor The patient mutters incoherent phrases in a voice almost inaudible Delirium continuous or inter mittent is passive although crises of excitation may occur When quiet patients lie immobile lethargic although conscious with the eyes half closed and fixed the mouth half open the relaxed facial musculature giving an expression of apathy or resignation This appearance may change into that of a profound intoxication of fatal prognosis

More commonly in the actively sick the face is congested and swollen the eyes brilliant sunken the conjunctivae injected the expression anxious restless and at times expressing pain or fear When hallucinatory delirium with excitation occurs and the expression becomes menacing or terrified the sick person may go to the extreme of committing suicide or homicide Pa tients in this state often flee from their homes or hospitals

In very severe cases a lethargic or comatose state develops with a total loss of sensibility these are signs of impending death The plague *facies* therefore is neither uniform nor constant and depends in large part on the toxicity of the infectious agent

Difficulties in the motor system appear early or late and consist of trembling muscular spasms convulsions contractures and preagonic carphol ogy In other cases the *facies* is determined by the degree of muscular relax ation

Sensory alterations are variable and include cutaneous hyperesthesia dull ing of the sense of hearing (at times more apparent than real) speech diffi culty alterations in the sense of taste intense thirst etc

Obviously plague has multiple nervous manifestations In India and China types with delirium and stupor are the rule In Africa and especially in South America these symptoms are lacking in the great majority of cases The classical descriptions of the Black Death of the Middle Ages are surpris ing in view of the number of curious nervous symptoms then described but which are not now seen

Cutaneous lesions of bubonic plague may occur early or late with very distinct pathologic significance Primary cutaneous plague the lesion of

becomes umbilicated breaks and dries forming a blackish scab finally a pustule is formed which drains a watery liquid The gangrenous center of the ulcer is dark colored and hard whereas the borders are raised and clear cut violaceous with surrounding edema

The primary carbuncle precedes the bubo by one or more days or is simultaneous with the bubo *and is usually localized near the ankles or wrists It* has been frequently observed in some Peruvian epidemics though totally absent *in others it has a benign prognostic significance*

In the course of the disease cutaneous manifestations are general (dry and burning skin or in very toxic cases a cold and pallid epidermis) or localized the latter being the more important although they are seen only in certain epidemics and in certain regions being notably absent in others The lesions seen are petechiae ecchymoses pustules (varioloid) and gangrene They have been given the general term "carbuncle Petechiae of variable size may appear over the buboes or independent of them especially on the abdomen or extremities They are dark similar to the ecchymoses which distinguishes them *from the generalized pustular plague eruptions that at times* resemble smallpox (plague variola) More often dark pustules (carbuncles) *appear after the development of the bubo are not very numerous and occur* in any part of the body and in any period of the disease These lesions may develop like the primary plague carbuncle *with a tendency to scarring or* they may extend into the subcutaneous tissues and involve a large inflamed area with necrosis from the central depths to the surface leaving a leathery indolent ulcer with firm edges and of varying depth and size When they exceed the usual size which is from 2 2 to 5 cm in diameter they may expose the aponeuroses the muscles and even the bones These great necrotic cutaneocellular ulcers occur most often in the gluteal and scapular regions Their prognosis is generally benign

The late pustular eruption is due to emboli of plague bacilli of low toxicity The late developing plague carbuncle is rare in South America but such is not the case with the so called "plague smallpox or plague variola *which has been reported in Chile* (1903) and very frequently in Ecuador

It is not uncommon to see extensive necrosis of the skin at the sites of the lymphatic glands accompanied by petechial eruptions circulatory disturbances (elephantiasis) marasmus etc *usually with fatal termination*

Of all the symptoms and clinical signs of bubonic plague the most important are those related to the **bubo** an indication of involvement of the lymphatic system In so called ambulatory plague the bubo may be the only sign of disease In the disease *ingua de frio* (cold bubo) of Brazil which corresponds to this type we have proved bacteriologically its plague etiology (1941) Epidemics of ambulatory plague have been observed in *the north* east of Brazil and in Ecuador The so called benign plague formerly called *pestis minor* or *aura pestilentialis minor* or *minior* is more frequently seen *this* manifests itself by early vague symptoms—slight fever headache conjunctival

inoculation was clearly described during the Black Death and the Great Plague of London At the present time it is less common being observed usually in relation to benign epidemics (Peru) Many of the classical texts



Fig 1ȷ4 —Plague cacl x a Typical bubonic case n tiated months prior to the photograph Left femoral bubo suppurated leaving indolent ulcer Generalized cutaneous petechiae and ecchymoses Interference with lymph drainage in right leg

of recent times do not even describe it It begins as a red macule which becomes papular and spreads with the center taking on a blackish hue (plague carbuncle) In the center a phlyctenule develops filled at first with clear serum which later becomes hemorrhagic and at times purulent The vesicle

described in which the tissue loss is so extensive that cavities are formed in which may be seen vessels nerves or bone

The most important localizations of the buboes are

1 In the inguinal region either near the crural arch (inguinal buboes) with the axis directed obliquely toward the middle line and downward or in any part of Scarpa s triangle (femoral or crural buboes) with the axis vertical Inguinal buboes may be partially intra abdominal The periglandular edema often extends to the abdominal wall or down the thigh as far as the knee *Even in the benign ambulatory cases it is possible to detect the infected persons by noting the limp corresponding to the extremity in which the bubo is located*

2 Buboes may occur in the iliac region The diagnosis is difficult when there is no accompanying inguinal bubo cases have been mistakenly diagnosed as appendicitis and patients subjected to operation (Macchiavello 1932)

3 Axillary buboes are usually accompanied by an extensive soft edema which advances from the breast as far as the neck and toward the deeper parts which may interfere with respiration The patient lies on his back with the arm abducted from the trunk Many times involvement of the subpectoral glands favors secondary pneumonic localization (Gaud and Jorge 1933)

4 Cervical buboes may be retroauricular submaxillary supraclavicular etc Edema is variable and may be almost absent or very extensive reaching the face or the thorax and at times involving the larynx and pharynx Two types of cervical glands must be distinguished *with relation to their origin* and prognosis those which arise from *tonsillar plague* or *plague angina—very frequent in the sierra of Ecuador* (Martinez Vinueza 1930) among the Indians who kill fleas and lice with their teeth—cases which commonly terminate in pneumonia and in which the tonsillar inflammation is enormous (de Souza 1913 Brites 1922) and those which derive from a cutaneous point of entry these are evidently more benign

5 Epitrochlear and popliteal buboes are less frequent and usually occur in cases with multiple localizations

Double and symmetrical buboes are a frequent finding At times they are multiple located in different places they may appear simultaneously or one after the other in neighboring or widely dispersed areas the former due to lymphatic progression of the infection and the latter to hematogenous spread

Of the types with multiple localizations note the syndrome described by Macchiavello (1941) called multiglandular plague fever It is characterized by a septic fever curve attenuated plague bacteremia *and a secondary septicemia* caused by nonvirulent microorganisms The course is prolonged for a month or more *during which time there appear* successively from 4 to 14 or more variously situated large buboes There are alopecia cachexia and slow *recuperation* with a prolonged convalescence or death may follow

congestion dizziness and vertigo—the significance of which is made clear by the appearance of the bubo although this is not accompanied by much pain nor by the characteristic inflammation In a week or ten days the bubo is reabsorbed or suppurates or becomes indurated A chronic form of benign plague was seen in northeast Brazil (1941) the buboes whether suppurated or not or whether softened or woody showed periodic inflammatory exacerbations which did not interfere with the patients occupations although they *caused a certain degree of debility and anemia In pestis minor the patient may be ambulatory or may take to his bed for one or two days rarely longer*

In grave cases the bubo is a notable sign which may usher in the clinical course even before a rise in temperature Commonly however the bubo occurs simultaneously with or later than the fever and it may appear very late The patient feels a sharp pain in the lymph gland area where the bubo will develop a pain which may be so intense as to mask the other symptoms Soon one or more enlarged glands appear which separated at first soon fuse into a single mass which makes up the bubo a mass which grows slowly or rapidly reaching variable sizes from the size of an almond to that of an orange usually about the size of a walnut or a hen s egg The smaller buboes are usually more painful and serious Around the bubo there develops an inflammatory zone of varying size it is hot hard reddened edematous and painful to the slightest touch Soft edema and mild inflammation usually accompany the largest buboes The inflammatory edema reflects the periadenitis and subcutaneous congestion which at times develop into a bloody effusion This entire *clinical picture requires one to five days for development and usually* daily changes in its evolution are noticeable

The shape of the bubo is oval or round the surface is irregular At first more or less free in the subcutaneous tissues it soon becomes fixed and adherent to the neighboring tissues The superficial consistency is pasty deeper it is firmer Over the bubo the skin is smooth tense red hot swollen and does not crease Rarely in South America but more often in other countries there appear over the bubo hemorrhages and phlyctenules carbuncles petechiae processes which occasionally go on to ulceration and gangrene Deep buboes and large superficial buboes are usually accompanied merely by a simple local sensitivity on palpation or pressure After a variable number of days the inflammatory signs and pain diminish the bubo softens or indurates or is reabsorbed or breaks down and suppurates When reabsorption takes place the pathologic process has a sequence inverse to that occurring in its formation leaving as a residue indurated glandular tissue and pigmentation of the skin When induration takes place the entire gland becomes woody or perhaps only one part or several parts which alternate with zones which are more or less soft or softening In cases of suppuration the skin becomes thinned over the gland which opens spontaneously between the seventh and fifteenth days draining a granular pus for a variable time in ordinary cases from 10 to 15 days In other cases the suppuration may last one or two months and is accompanied by tissue necrosis of varying degree cases having been

Renal manifestations in the course of bubonic plague are inconspicuous and usually are overlooked. The urine is scanty, highly colored, low in chlorides and urea, with albumin and at times cylindruria and even hematuria. Retention of urine is seen rather frequently, but anuria is *exceptional*. *Elimination* of plague bacilli in the urine has been reported.

Evolution and Termination

Bubonic plague usually has a course of 6 to 8 days if it does not terminate fatally. Between the sixth and seventh days the fever may recede accompanied by sweating, with favorable changes in the *facies* and in the general condition, pulse rate, and psychic manifestations. Buboes which have sup*purated heal with scarring* between one week and a month. Convalescence does not always accompany improvement in the symptoms, the patients often continuing in a debilitated condition although afebrile. There is very often a false impression of improvement, but the pulse soon becomes rapid and small, fetid diarrhea begins, and dyspnea, sweating crises, insomnia, apathy and *weakness are all increased. The buboes drain an abundant fetid pus* without any tendency to scar formation, the patient finally dies after the twentieth day.

Death nevertheless usually occurs within the first few days. In fulminating cases it may occur in 12 to 24 hours, in grave cases in from 2 to 3 days. Death usually occurs before the sixth day from toxemia, cardiac failure, cerebral involvement, or secondary causes such as hemorrhage, asphyxia, etc.

A certain number of cases of bubonic plague in one epidemic or another develop a secondary plague septicemia. *It is possible that all bubonic cases* except the ambulatory develop a plague septicemia or bacteriemia at one or another period.

Complications

Complications are frequent, and a few, as the pulmonary, are exceptionally important. They include pulmonary edema, bronchitis, pleurisy, *pneumothorax*, and above all secondary pneumonia. The origin of this secondary pneumonia is as follows: *Past. pestis* reaches the lungs from any *lymphatic* region; it enters the thoracic duct and passes into the left subclavian vein giving rise to pulmonary emboli which act as a substratum for focal broncho*pneumonic processes, at times* becoming confluent with a secondary plague pneumonia. Usually this process requires a bacterial strain of great *invasive* power and slight toxigenicity, combined with a lengthy survival time of the patient. *It is a fact that the secondary pneumonias* appear late in bubonic cases of mild evolution, and under circumstances which *facilitate the* extension of the infection by way of the lymphatics, such as physical exercise. Macchiavello and Uriguen *(1944)* have reported experimental proof of the foregoing. Additional complications which have been *described include* gastrointestinal upsets, abortion with death of the fetus, arthritis, conjunctivitis, *corneal ulcer*, various hemorrhages, chronic plague, and *marasmus*. By



Fig 15 Inguinal bubo Common plague facies

Similarity to yellow fever can be judged from the fact that often in dealing with these cases the Brazilian Yellow Fever Service has been mistakenly requested to control yellow fever

We have recently been able to confirm the existence of benign or ambulatory cases of plague septicemia (Peru) characterized by the absence of buboes a feeling of intoxication oneiric delirium and at times fever which does not last more than one or two days The usual diagnosis of these patients is benign grippe but blood cultures revealed the presence of very attenuated strains of plague bacilli

PRIMARY PLAGUE PNEUMONIA

Primary plague pneumonia is even more serious than plague septicemia In epidemics it spreads from person to person either by direct contact with individuals engaged in the commercial handling of skins of wild rodents in areas where sylvatic plague exists or from an original case of secondary plague pneumonia in a bubonic case Transmission occurs from person to person by droplet infection The evolution may be fulminating with death in a few hours or death may occur between the second and fifth day of sickness the average survival time (Wu Lien teh 1936) in the epidemic at Harbin being 1 8 days in 1 128 cases The clinical aspect depends on the gravity of the infection but in general the patient does not lose consciousness even when delirious Symptoms and signs observed most frequently are fever which remains high until death malaise restlessness a feeling of retrosternal constriction cardiac failure and terminal cyanosis The pneumonia is indefinite difficult to auscultate and percuss and lobular at the beginning although it may become lobar later The paucity of physical signs is in contrast to the grave clinical picture even when in reality the patient does not appear to be suffering (Wu Lien teh 1926) The principal signs are cough with a scanty viscous blood tinged sputum which later becomes more fluid bright red and loaded with plague bacilli (Murdock 1939) The contagiousness of these cases is enormous after a noninfectious period of 24 to 48 hours (Zabolontny) when the cough has not yet begun The mortality is practically 100 per cent so that one doubts the diagnosis in any case in which the patient recovers The diagnosis in early cases may be suspected when one encounters a patient with an atypical pneumonia and in whom the dyspnea and marked tachycardia and at times the gravity of the clinical picture cannot be explained on the basis of insignificant pulmonary signs

DIAGNOSIS

The diagnosis of plague in any of its forms is simple if the existence of plague in the locality in epidemic or endemic form is known Nevertheless every time plague has invaded a country it has given rise to extensive debate The initial clinical picture of bubonic plague can be confused with any acute infection The bubonic forms require differential diagnosis from other glandular diseases especially those of acute venereal origin Primary plague septi

marasmus we mean a progressive emaciation accompanied by stupor and profound weakness On the other hand in chronic plague the patient has apparently mild symptoms but may die with visceral abscesses in the spleen liver or lung similar to the chronic plague of rodents The buboes may be complicated by secondary pyogenic infection abscesses skin furuncles A true plague meningitis has been seen on rare occasions (Lafont et al 1915 Paso 1925 Godinho 1907 Sauhueza 1907 Meyer et al 1937

The sequelae of plague are nearly always temporary and related to the nervous system (aphasia dementia ataxia) to the skin (gangrene) or to the sense organs (blindness)

An attack of plague is supposed to leave a permanent immunity Simpson however (1905) cited several cases of a second attack with the second not always the more benign some cases terminating fatally

PRIMARY PLAGUE SEPTICEMIA

Cases without buboes, and with *Past pestis* present in the blood stream are held to be **primary plague septicemias** They are generally more serious than the bubonic cases Many cases catalogued as septicemic have deep buboes which are typical but which are not diagnosed during life In true plague septicemia the glands are slightly hypertrophied and inflamed as a consequence of the generalized hematogenous infection However the blood stream invasion may be so sudden and acute that the sickness may end in death even before 24 hours with no involvement of the lymphatic system Most commonly the clinical aspect is the same as that of a grave bubonic case with numerous nervous symptoms and no bubo In very toxic cases the temperature is moderate the facies pallid the general aspect anxious or stuporous with a thready pulse and intense dyspnea after a final period of coma with relaxation of the sphincters carphology etc the patient dies But few cases of typical plague septicemia recover at times a late bubonic localization occurs secondarily and all symptoms regress until recovery takes place The percentage of septicemic cases in Asia is quite high—up to 30 per cent In America the primary septicemic form is exceptional and at most includes less than 5 per cent of the cases

So called **gastrointestinal plague** which is related to the septicemic form includes various types Hojel in Bombay described a typhoid form with epigastric pain abdominal tension rachialgia hypertrophy of the liver and spleen abdominal petechiae a typhoid state and involvement of Peyer s patches without concomitant lesions in the mesenteric glands Wilm, in 1896 in Hong Kong described a violent gastrointestinal form accompanied by mesenteric gland involvement but without external buboes In Brazil in 1941 we saw an amarillic form apt to be confused with yellow fever because of the icterus the color of the vomitus and the general symptoms which were especially violent in the digestive apparatus (hemorrhages hematemesis melena vomiting and violent diarrhea) with complete absence of buboes

doses (100 cc intravenously followed by one or more similar injections at 6 hour intervals if necessary) Serum improves the general condition of the patient and lengthens the average survival time but usually it does not prevent a fatal outcome except in a small percentage of cases The serum therapy has proved of no definite value in South America and at times there is a higher mortality among the plague patients treated with specific serum than in the control cases and a very high incidence of anaphylactic phenomena similar to serum sickness We do not advise the use of serum except in grave cases treated before the second day of the disease excluding the septicemic and violent pneumonic forms in which we feel that serum is useless

Penicillin in the treatment of plague has not been extensively studied This also applies to streptomycin although Hornibrook (1946) has obtained promising experimental results in plague mice He also found that streptomycin inhibited the growth of *Past pestis* in broth in a dilution of 1 160 000 A preparation containing 200 000 units per gram was used It was tested by Sokhey with excellent results in India (1948)

PROPHYLAXIS AND METHODS OF CONTROL

From the epidemiology and the clinical course of plague it can be concluded that methods of prophylaxis and control should be based on one of the following points methods against rodents methods against fleas and methods relating to human beings sick or well In all countries where plague is an important sanitary problem these methods are under the jurisdiction of official services of public health and many of them have been incorporated into international conventions (the International Sanitary Convention of Paris 1926 with the recent modification under the auspices of UNRRA and the Pan American Sanitary Code which include the early agreements of the Washington Convention 1905)

The methods used against rodents vary considerably, depending upon whether one is dealing with wild or domestic species Since the living habits of the former are so variable it is not possible to outline a general plan of action but trapping poisoning shooting destruction of burrows fumigation etc may be found useful In certain regions it may be advisable to provide direct means of individual protection as in the case of persons hunting for skins and others who for whatever reason must come into direct contact with these rodents

Antirat procedures include all measures used to make buildings and dwellings rat proof

Deratting measures may be applied in any situation where the destruction of rodents is necessary such as ships ports cities fields and sylvan areas The principal methods of deratting are fumigation (which by certain methods destroys fleas as well) trapping and poisoning

Fumigation may be performed with carbon monoxide ethylene bichloride sulfur derivatives (sulfurous anhydride) and especially with hydrocyanic acid which may be made in situ with potassium or sodium cyanide and sulfuric

cemia may be suspected but not proved clinically without bacteriologic confirmation This also applies to plague pneumonia

Definite diagnosis is usually made by means of the specialized public health services For those who wish to make their own diagnoses the suggestions we have recently made (1945) concerning the identification of *Past pestis* and the procedure of Webster transcribed by Wu Lien teh et al (1936) are recommended In general definite diagnosis is based on the presence of *Past pestis* in the suspected material—lymph gland pus blood or sputum—which may be detected by direct examination of stained slide by inoculation into susceptible animals (guinea pigs are most useful) and by culture A combination of the three methods is preferable

PROGNOSIS

In India the bubonic form has a mortality rate of 60 to 90 per cent in America it can be as low as 15 per cent although usually it is around 35 to 40 per cent The septicemic form has a mortality rate of 90 to 95 per cent and the primary pneumonic form 100 per cent

TREATMENT

Up to the present time the nonbiological treatment of plague has been ineffective except for symptomatic measures—rest in bed cleanliness purgation hydrotherapy in cases with hyperpyrexia antipyretics when there is no cardiac involvement cardiac tonics morphine as a sedative etc The sulfonamides recommended by Schutze (1939) Carman (1938) Chopra (1941) Villafañe Lastra et al (1941) Plum (1942) Burga Saavedra (1942) Wagle et al (1941) Sokhey (1940) Savino and Morales Villazon (1942) Durand (1939) Girard (1941) Wayson and McMahon (1944) etc both in experimental animal plague as well as in the human disease and especially sulfathiazole and sulfadiazine appear to give good results in bubonic and septicemic plague At the present time sulfadiazine is recommended we have had even better results experimentally with sulfamerazine A sufficient dosage must be given to maintain a sulfonamide blood level of 15 to 20 mg per cent during the first 4 or 5 days of the disease The initial dosage recommended should be equivalent to 4 Gm (60 gr) of sulfadiazine with subsequent doses of 2 Gm every 4 hours day and night until the fever drops and thenceforward 0 5 Gm every 4 hours until the fifteenth day The author (1946) is of the opinion that the statistics collected in South America on the value of treatment are not very convincing and believes that in many benign epidemics drugs have been applied so indiscriminately that part of the mortality is due to abuses in treatment

With regard to the biological treatment of plague the use of bacteriophage has proved to be ineffective With regard to the use of hyperimmunized horse serum in plague (antiplague serum) we personally share the point of view of Chosky that it is useful only when applied early in large

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acid, or purchased in a liquid state in steel cylinders, or absorbed in aluminum earths or on special paper discs, or in the form of calcium cyanide

Eradication also can be accomplished by toxic gases applied to the rat burrows (calcium cyanide) or by the use of flame throwers, introduced by Donovan and Hopkins in cooperation with Long (1941) Traps of the snap or "guillotine" and wire cage type are used

Poisoning is carried out with baits attractive to rats flour, fish, fruits crackers, liquids, etc The continual use of the same bait as a vehicle renders it ineffective, since the rats stop eating it in a few days The poison used preferably is white arsenic in 18 per cent strength In other places the use *of phosphorus has become more popular (Darvault paste,* Danysz paste, Schattermann's poison etc) barium carbonate, red squill, strychnine, potassium cyanide, thallium sulfate, and gypsum (which acts by hardening in the rat's stomach) We believe that the introduction of sodium fluoroacetate called "1080" (a rat poison developed by North American investigators), opens a new path in rodent poisoning (Ormsbee, 1945, *Johnson*, 1945, Kalmbach, 1945)

Methods against fleas include many of those employed against rats such as flame throwers *in* rat burrows *and* on floors, cyanogen gas *in* rat burrows, hydrocyanic acid gas on ships etc Repellents have also been used, such as kerosene, cresol, and others, all of which are of only temporary effectiveness The introduction of DDT (Zeidler, 1874 Muller 1939 Orlando Laboratories, Florida, 1944) has opened a new field in the fight against the vector of plague Similar new *insecticides* such as Gammexane or "666," the gamma isomer of hexachlorocyclohexane, have similar effects (Slade, 1945)

Working in cooperation with the National Anti Plague Service of Peru, the author has applied to the prevention and control of plague the two most powerful arms which we have at the *present* time as insecticides and rodenticides, respectively—DDT and "1080" or sodium fluoroacetate. "1080" and DDT may be used advantageously as well in the control of sylvatic plague Another poison recently introduced, which appears to be effective especially against *R norvegicus*, is alpha naphthyl thiourea (ANTU), a drug which in small doses produces a marked serosal exudation into the thoracic cavity The repeated application of this poison produces a high degree of tolerance It acts as a contact poison as well as by ingestion (Richter 1945) McClosky and Smith *have studied the pharmacology of this chemical* (1945)

Methods used with relation to human beings vary, dependent *upon* whether one is dealing with well people or with patients sick with plague Personal prophylaxis consists in (1) Avoidance of the infection (2) Protective vaccination either with suspensions of avirulent living microorganisms (the vaccines of Otten and of Girard) *or* with vaccines made with killed plague bacilli (especially the Haffkine) This *is* not the place *to discuss* the value of these procedures, but if they are used, the recommended dosage must be employed according to the indications (3) The application of antiplague serum as a preventive We believe that this last procedure should be reserved exclusively for very special cases, since the reactions caused by the *sera, at least those available in South America*, are often severe

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which this expression suggests) Each epidemic inspired additional concepts of the etiology, as when Scott, in 1832, decided that a soldier in his command "generated this disease within him by a fit of intoxication," and that it was "intemperance which generates and spreads the calamity" (Phalen, 1942) Snow (1855) collected evidence of the distribution of cases in London which pointed directly to the cause in water supplied from a certain pumping station and did not hesitate to draw conclusions He was perhaps the first investigator to demonstrate that water, rather than air, was the medium of transmission Scott (1939) refers to a discovery by Pouchet, as early as 1849, of vibrios in the stools of cholera patients The definitive demonstration of the cholera vibrio is attributed to Koch (1883) Unfortunately it was attended by considerable disbelief and confusion owing to nonpathogenic vibrios which were also detected and some matters such as the real significance of the El Tor vibrio, remain disputed by bacteriologists to the present day

The earliest efforts to treat cholera utilized anything that could be conceived to have virtue, from drugs to physical therapy, and while a certain proportion of victims survived both the disease and the treatment, there was and is nothing to suggest that anything was gained Saline, however, was injected as early as 1831 by Thomas Latta (1831 1832) Doubtless the dosage was insufficient in these early trials else the importance of fluid would have been appreciated half a century sooner It was not until 1909 that Rogers (1915) used saline in the amounts now generally employed, which alone has been the decisive feature of treatment as it remains today The 1947 epidemic in Egypt gave opportunity to try a great number of sulfonamide derivatives, several of which seemed to reduce mortality somewhat when given early enough in the course, although statistical proof is not striking, but even then it was obvious that Latta's treatment was the indispensable determining measure In the 1947 epidemic, also, there was demonstrated a specifically effective method of restoring kidney function in uremic subjects with testosterone and, in consequence of this, in such cases there was what some have regarded as an outspoken reduction in mortality

From the seventh century to the present day, cholera has existed in the region of the Ganges delta and has been disseminated from there to the entire world Effective measures have almost entirely excluded it from the West and much of Europe but the Near East continues to suffer periodic outbreaks, supported, probably, by now well established local stores of the vibrio Transmission of the disease is so well understood and is nominally so readily subject to effective control, that one might expect that the disease would have been eradicated for all time in India and eventually in the entire world That [illegible] explained freely in various ways, and there are even tho[illegible] as a source of relief from "overpopulation" Tw[illegible] newborn, have the opportunity to succeed on their own behalf where for centuries others have failed, and the next few years will show whether in time to come there might not cease to be such an appalling thing as epidemic cholera

ETIOLOGY

Vibrio comma is a bacterium of the order Eubacteriales, family Pseudomonadaceae, which includes only the vibrios and Pseudomonas as of clinical interest (Breed et al, 1948) Of its tribe, Spirilleae, vibrio is the only known pathogen and although vibrios are quite numerous, only one pathogen *Vibrio comma*, is recognized This species has been divided into three strains Inaba, Ogawa, and Hikojima, the virulence of which is undisputed, but it also includes "another vibrio" known as El Tor, which has appeared at times as a pathogen beyond doubt, and at other times as an object of terrible perplexity (Linton 1940)

CHAPTER 28

CHOLERA (ASIATIC CHOLERA)

EDWARD HENDERSON AND HARRY SENECA

DEFINITION

Cholera is an acute, infectious, systemic disease caused by a specific organism, *Vibrio comma*, and characterized by an overwhelming diarrhea, nausea, and vomiting, followed by dehydration, medical shock, and renal insufficiency, with a dramatic course and high mortality It is endemic in parts of the Orient, particularly India and China, and has appeared in epidemic form in many other parts of the world

Synonyms—Various terms which refer to cholera in general are Asiatic, Indian, epidemic, malignant, pandemic, spasmodic, and pestilential cholera Old clinical terms such as asphyctic, algid, typhoid, and automatic cholera refer to clinical forms in which the several manifestations seem to predominate A less acute disease which has been attributed to other vibrios is known as bilious, European, simple, or sporadic cholera, or *cholera nostras* Unfortunately the name *cholera* has been loosely given to numerous diarrheas of impressive severity, none of which is cholera, hence we have "winter" and "summer" cholera, *cholera morbus* (acute gastroenteritis), and *cholera infantum* (summer diarrhea in children)

HISTORY

An early description of diarrheal disease attended by very high mortality occurs in the Indian writings of Susruta in the seventh century One naturally looks to India for early recognition of this disease However, other enteric diseases doubtless depopulated the ancient world if not nearly so well as cholera and none of the historic descriptions of epidemic diarrhea, prior to the nineteenth century, wholly rules out other diagnoses During the nineteenth century, the world was shaken by repeated, authentic pandemics of cholera which originated in India and traveled by land and sea routes throughout Asia, and, aided by religious pilgrims and the Suez Canal, throughout Europe and as far as the United States Napier (1943) presented a map of the world in which is traced the course of travel of two of the early epidemics

The first pandemic began in 1817 and extended to Asiatic Russia, Persia, Arabia, Ceylon, and the Far East The next, in 1826, involved, in addition, all of Europe (1832) and localities in the United States (1836 1838) Successive pandemics originated in India in 1842, 1863, 1879, 1891, and 1902, and each spread widely, but thereafter effective control measures were instituted by many countries and cholera ceased to be world wide No outbreak occurred in the United States after 1873, and quarantine in this country was effective from 1911 Elsewhere the disease continued to flare, as in parts of Europe and especially Russia, and in the present century small epidemics have been seen in the Philippines as recently as 1935 1936 The most recent notable epidemic (anonymous, 1947) appeared in Egypt in 1947, it consisted of more than 20,000 cases, with an admitted mortality of 48 per cent

The disease was long attributed to a poison of oriental origin, transmitted by the air, i e, a miasma (In the Arabic language, cholera is called *hawa asfar*, "yellow air" Apparently the ancient Arabian physicians associated the disease with filth, decay, etc.,

1947), but not conclusively (Gohar, 1948b) Butter appears definitely to have transmitted the disease (Grattan, 1939) Likewise the question whether or not vibrios can survive in the soil, and under various climatic conditions, has been studied (Sanyal, 1941), and it has been concluded that moist soil containing an optimum concentration of nitrates and organic matter is capable of harboring the organism for long periods

Variation

Like many other organisms, the cholera vibrio readily becomes adapted to any environment in which it can survive at all Sufficiently prolonged cultivation, as upon laboratory media, yields organisms differing in carbohydrate and protein composition from the parent strain, that is, "variants" If specific antisera are contained in the medium, the serologic specificity of intact, virulent "smooth" organisms is abolished, and there result the metabolically inactive, more generalized, "rough" forms Phage has a similar effect. An extensive literature has classified the native vibrio (as obtained from patients with cholera) and its subsequent variations, using metabolic and serologic criteria That such variations are equally possible in nature must be emphasized They would explain the progressive increase in virulence during an epidemic and the change from low to higher virulence in carriers.

Immunologic Types (Heiberg 1935, Linton, 1940) —The original or Inaba vibrio is accompanied even in the same epidemic by the Ogawa type or variant (Felsenfeld, 1939b Pasricha, 1942, Soman and Naik, 1945), as well as the "intermediate" Hikojima type (Fournier, *1940*) In any collection of vibrios (Burrows et al, *1946*) or in vibrios collected in any one region (Felsenfeld, 1939b), there is found a varying proportion of each of these, together with El Tor vibrios The fact that not all El Tor vibrios fall in the O antigen group I has been mentioned, notwithstanding the group I antiserum has practical diagnostic value as revealing some 85 per cent pathogenic strains (Taylor, 1936) This method of typing has been carefully studied (Burrows et al, 1946) The possibility remains however, that any type may change over into another, and what have been regarded as types may not be more than variants (Shrivastava and White, 1947)

The El Tor Vibrio

Older literature discusses at length whether this vibrio is ever a pathogen It is a proved cause of clinical cholera, in localized epidemics, as in Celebes (DeMoor, 1938, 1939, van Loghem, 1938) in 1938 and 1940, and in East Africa (Marras, 1938) It makes slight difference practically whether such outbreaks are termed "choleriform" merely because the organism is more hemolytic than expected of a proper cholera vibrio—especially when the metabolic and serologic criteria conform so closely

The El Tor vibrio may be pathogenic in one locality and not in another (Abdoelrachman, 1944, 1945) It may include "types" within its "type" (van Loghem, 1946) It *has repeatedly been described (Read and Pandit, 1941*, Venkatraman et al, 1941) as occurring in the absence of clinical cholera, in patients having food intoxication (Kato 1941) and in patients with gastroenteritis, which it may have caused (Felsenfeld, 1939a) *Thus* it is not unreasonable to think of this vibrio as a type of *V comma*, susceptibility to which varies more greatly than to the other types The occurrence of epidemic cholera proves that the susceptibility of the host, and the virulence of the El Tor vibrio, can reach the same degree as with other *V comma*

The hemolytic power of the El Tor vibrio, on which its identification relies in part, is generally greater than that of the so called nonhemolytic vibrios but the distinction is far from absolute Even recognizing the difference between "true hemolysis" (van Loghem, 1938, Bernard et al, 1939, Felsenfeld, 1944, Gohar, 1932, Kabeshima, 1918, Mertens and Beeuwkes, 1940, Read et al, 1942) and "hemodigestion" (Read et al, 1942), the hemolytic action that will be seen depends on the detailed technic used, the age of the culture, its history since isolation from the disease, and peculiar properties of the blood that is used (Otten, 1939) A "true" vibrio which has not grown in the laboratory for more than a

Synonyms—Koch's name for this organism was *Kommabacillus*. It is frequently designated by the specific names *comma*, *cholerae*, and *cholerae asiaticae*, thus *Spirillum cholerae asiaticae*, *Pacinia choleraeasiaticae*, *Microspora comma*, *Vibrio cholerae*, *Bacillus cholerae*, *B. comma*, or colloquially simple as the cholera vibrio.

Classification

At one time the effort to classify vibrios was concerned with the distinction between *V. comma* with some other chemically and antigenically similar vibrios and "other vibrios" of no clinical importance—so called groups A and B respectively. A tremendous amount of work has now reduced the problem to vibrios which although they have a common H antigen, can be distinguished by their O antigen as belonging to group I of a possible six groups (Gardner and Venkatraman 1935). Group I includes vibrios not hemolytic to goat or sheep cells, that is, "true" *V. comma*, and vibrios which are hemolytic, or at least more markedly and permanently hemolytic, than the preceding, that is, the El Tor vibrios. Unhappily, some El Tor vibrios are described within the other O groups, but this is not the only source of difficulty with this type strain or variant whichever it may be.

Morphology and Colonies

The cholera vibrio is a slightly curved rod 0.5 by 1 to 5 microns observed singly and in chains which tend to be spiral. It is gram negative and motile and has a single terminal flagellum. It forms small (1 to 2 mm), circular, slightly convex, moist, glistening, translucent colonies on solid media. These are yellowish white on gelatin, brownish white on agar and colorless (or later pinkish) on MacConkey's medium and are surrounded by a small zone of "hemodigestion" on blood agar. In broth there is a slight turbidity and also a flocculent precipitate with wrinkled pellicle. Gelatin is liquefied.

Reactions—It forms acid but not gas from glucose, fructose, mannose, galactose, maltose, sucrose, mannitol and (slowly) glycerol but not from lactose, arabinose, inulin, or dulcitol. The combination mannose+, sucrose+, arabinose− has been suggested (Heiberg 1935) as a determinant for *V. comma* but is not specific since the same type of reaction has been noted with other vibrios.

It is an obligatory anaerobe living at an optimum temperature of 37° C and an optimum pH of 7.6 to 8 with poor tolerance to an acid medium.

It forms indole and nitrite from nitrate and thus it gives the *cholera red* reaction provided reducing agents such as carbohydrates are not present in excess (Sen et al 1946). Hydrogen sulfide is formed. Starch is hydrolyzed actively at high pH. It is Voges Proskauer negative.

Resistance

To proliferate the vibrio must have water, salt and organic matter. It has been stated that it is easily (Napier 1943) or readily (Kahn 1942) killed by drying, nevertheless vibrios have been found viable four years after having been dried and sealed. The vibrio is also killed by overgrowth of other organisms as in water containing sewage. Optimum conditions appear to be about 1 per cent salt and 2 p p m peptone but the organism can survive for weeks in concentrations one tenth of these or less. It does not withstand temperatures above 42° C or below 14° C nor pH below 6 (nor it is said, above 9.4). Heating at 55° C destroys the vibrio after 15 minutes. The usual organic (phenol) and inorganic ($KMnO_4$, $HgCl_2$) poisons destroy it rapidly. Numerous races of bacteriophage including the specific races A and N, destroy the cholera vibrio.

Water in tanks is more conducive to survival of the vibrio than free running waters. Water which has been sterilized by autoclaving enables it to survive for 3 days or more, utilizing probably organic material which has been thus broken down (Lahiri et al 1939). *Foods of many kinds have been studied to determine whether the vibrio can remain viable* within or upon them, or can be transmitted by them. Dates have been considered (Yen,

conditions permit, until a *number of "animal passages"* have taken place in the human population. Some of the subjects may be *in poor health*, or some may be susceptible enough to experience a mild diarrhea, and the vibrios they discharge will have gained in virulence. Presently they *are found in sufficiently large* numbers to be detected in the stools. Soon the infecting dose and the virulence are sufficient to produce recognizable cholera *in a few persons*. *From this point the* extent of an epidemic is limited only by the facility with which vibrios can be transmitted *from one person to another*.

The carrier state is important in facilitating an unobserved transfer of organisms among *the population*. It is also important to the carrier himself, as antecedent to clinical cholera *at any time his* susceptibility may increase. Harboring the organisms does not confer immunity nor does clinical cholera preclude susceptibility at a later date. Carriers may show *no symptoms of the disease for a few days and yet later come down with the most overwhelming form of cholera*.

A person who is a carrier at one time may cease to show organisms and later again may *have them*. Whether this is necessarily the result of a reinfection, or whether the organisms *lurk in the intestine or gall bladder* so that the carrier state is actually much more prolonged than it seems, cannot be concluded. The situation is met in careful cholera control, by reexaminations of supposedly "negative" subjects.

Epidemic Characters

In India, the disease reaches its peak during the warm, rainy season when the humidity is high. As the humidity declines, the epidemic severity subsides until at 10 per cent relative humidity the disease reaches a standstill. This was likewise observed in Egypt.

The progress of an epidemic is related to the phage titers which are found. When phage is at a maximum, the epidemic comes to an end, while very low titers are seen during the height of an epidemic, when almost all vibrios isolated are typical and agglutinable. Vibrios surviving the action of phage become atypical, nonagglutinable, and, in due course nonpathogenic.

GEOGRAPHICAL DISTRIBUTION

The world distribution of cholera changes little from year to year; for many years it has been confined to India and the Far East, the exception is the appearance of epidemic cholera in the Mediterranean area such as the recent epidemic in Egypt. Cholera statistics are always somewhat unreliable (Seil, 1945). Reports vary in completeness but probably never exceed the actual incidence. Some districts may lack medical personnel entirely, and others may be reluctant to admit the presence of the disease even when it has been recognized since it is today a serious reflection on the very civilization that harbors it. Hence one may conclude that cholera is as prevalent as is shown, where it is shown to be prevalent, and one may suspect it to exist in any neighboring district, particularly when reports are lacking. The distribution, as it affects cities, might be misleading, since it is only in cities that cogent sanitary improvements exist, but cities necessarily have the burden of reporting many cases coming to them from outlying districts.

The division of India into Pakistan and India, while shown by boundaries, has no immediate influence upon the density of cholera throughout the region, and this has therefore been shown in a uniform manner.

Pilgrimages.—Since the turn of the century, cholera has been largely confined to the Far East, its spread westward to the Near East depends on religious pilgrimages to Mecca. Mohammedan pilgrims from India, the Far East, and the East Indies, where the disease is endemic, come in contact with pilgrims from the Near and Middle East and North Africa. When the latter group acquire the infection they give rise to epidemics on returning to their own countries. At present, persons going to Mecca are required to be vaccinated against cholera and when possible, to have negative stool cultures for the vibrio. Large numbers are examined on their return at the end of the pilgrimage, as they pass through government quarantine stations in Egypt, if no vibrios are isolated,

few hours *may* be strongly hemolytic, while after 24 hours the property may be lost, a so journ in artificial media is more prone to change the hemolytic power of "true" vibrios than of El Tor vibrios (Doorenbos, 1936, 1937) Thus, hemolysis is only an approximate guide to the identity of the vibrios, and new criteria would be most desirable in its stead These are being sought e g, lecithinase (Felsenfeld, 1944)

Mode of Transmission

Water is the principal offender, especially when latrines used by infected persons are so situated as to contaminate the water supplies of others Milk contaminated by unclean handling, vegetables contaminated by infected water, dates, and butter, as well as flies (Whitmore, 1929) which may convey vibrios from feces to food, have been mentioned. "Cholera nests," scattered groups of cases infected in such indirect ways, are thus explained Various insecticides such as DDT have been used during epidemics in an effort to eradicate house flies and other insects These may conceivably carry the vibrio (Felsenfeld, 1937) Even direct personal contact if sufficiently close and prolonged (as on board ship), may spread cholera (Whitmore 1929) Cockroaches and rats have been suggested as a method of distribution (Napier 1943) Some writers have expressed confidence in the safety of milk which has soured, since the vibrio does not flourish in an acid medium, but it has been shown that vibrios remain viable in sour milk for as long as 6 days (Whitmore, 1929) Food handlers harboring the vibrio must be thought of also as vectors

Pathogenicity

V comma is known to produce disease naturally only in man. Peritonitis can be produced by intraperitoneal injection of viable organisms into mice, guinea pigs, and some other small laboratory animals, and intravenous injections is fatal to rabbits, but these do not necessarily reveal the route taken by vibrios in clinical infection (Sanarelli, 1916), or even furnish a basis for evaluating vibriocidal drugs

The susceptibility of the host is variable and is obscured by such factors as the number and virulence of the organisms reaching the gut The normal acidity of the gastric juice is thought to destroy most of the vibrios However, the deliberate swallowing of cholera cultures has led to every possible result from noninfection to fulminating disease and death Experience shows that impaired general health, and particularly gastrointestinal disorders, even including the use of a cathartic, predisposes to invasion by cholera vibrios The vibrios may have already been present (carrier state), and become invasive when the patient was malnourished, fatigued, intoxicated, ill with other disease, or, as it has been said, "worried" It may also be impossible to recognize a single predisposing factor in robust persons who acquire and succumb to the disease As with many tropical diseases, the newcomer is said to be more susceptible than the native, and while this may be apparent in other conditions it is difficult to imagine greater susceptibility than that among the natives, say, of India, who perish by the hundreds of thousands

Carrier State

As a rule a cholera carrier either is convalescent after cholera or is in the incubation period of the disease There is rarely a normal or healthy carrier, although low grade or subclinical infections occur Usually, the vibrios do not persist longer than 3 to 5 days after ingestion, either in patients or in carriers Exceptionally they may be present for 2 weeks, and periods as long as 3 and 4 weeks are mentioned It is regularly found (Wilkinson, 1943) that the carrier rate or proportion of subjects examined who show the vibrios, rises to 20 per cent just before an epidemic of cholera In view of incomplete knowledge of the transformation of vibrios from one to another "type," which occurs in the laboratory and also, from statistical data, in the field, it may not be important whether the vibrios are true pathogens Indeed at the outset of the process, they may theoretically be of low virulence, but then one visualizes the transfer of organisms from one host to another, as unsanitary

acterized by whitish shreds of desquamated epithelium ("rice water" stools). Microscopically these shreds contain cells which may be greatly deteriorated or are practically debris and mucus possibly with a few erythrocytes; there is virtually no sign of inflammatory reaction.

The central feature of the disease is the loss of so much body fluid in consequence of diarrhea and vomiting as to produce a state of medical shock (See Table XVI.) This includes hypotension, peripheral vascular collapse,

TABLE XVI. CHOLERA AND OTHER DISEASES COMPARED

(Presented in abbreviated form from Scudder, 1940)

THE BLOOD	CHOLERA	ADRENAL INSUFFICIENCY	ACUTE INTESTINAL OBSTRUCTION	SURGICAL SHOCK
Physical characteristics				
R B C	+	+	+	+
Hemoglobin	+	+	+	+
W B C	+	+ (Terminal −)	+	+
Specific gravity	+	+	+	+
Hematocrit	+	+	+	+
Total solids	+	+	+	+
Anions				
Cl	−	−	−	− (+)*
HCO_3	−	−	+ (−)*	−
HPO_4	+	+	+	−
SO_4		+	+	
Proteins	+	+	+	− +†
Total acid	−	−	−	
Cations				
Na+	−	−	−	−
K+	+	+	+	+
Ca++	+	+	+	+
Mg++	+	+	+	
Total base	−	−	−	
Nonprotein nitrogen (various criteria)	+	+	+	+
Blood sugar	+	−	+	+
pH	−	−	−	−

+ Increased; − decreased.
*Minority finding in parentheses.
†Depending on circumstances.

tissue dehydration and anoxia, acidosis and renal insufficiency. These features almost fully explain the clinical findings in cholera. It may be that the toxin directly damages the kidneys, as shown by albuminuria and casts and at autopsy by congestion and necrosis, but considerable renal damage can equally result from ischemia and the shutting down of glomerular filtration, so that under these circumstances the renal failure is of purely extrarenal origin. It is difficult in fact to identify a feature of the disease that can be attributed to the distribution of a toxin, the one exception being the *sicca* variety of the disease.

Organs Other Than the Intestine

The vibrios make their way, no doubt via the portal system of veins and the lymphatics, to the liver and biliary tract and are often observed in the

the group is declared free of cholera and all are permitted to depart while if vibrios are found, strict quarantine measures are enforced During the past 15 years a new automobile route was authorized for pilgrimages from Baghdad through the heart of Arabia, to Mecca In 1938, Seneca isolated an El Tor vibrio from a Persian pilgrim returning from Mecca through Iraq to Iran

The Egyptian epidemic of 1947 was produced by vibrios introduced by British soldiers proceeding from India to England

The Ganges River is sacred to the Hindus During pilgrimages the devout bathe in the river and the disease acquires epidemic fury It is reported that when the ashes of Mohandas Gandhi were committed to the river this occasioned bathing by a great many persons, which was followed by the occurrence of several hundred cases of cholera

PATHOLOGY

The disease process in cholera begins with the multiplication in the alkaline medium of the small intestine of so many vibrios as have survived passage through the stomach They may barely sustain themselves and no



Fig 156—Intestine in Asiatic cholera showing denudation of the epithelium round cell infiltration edema of the submucosa Low power magnification (×100) (Courtesy of Oscar Felsenfeld) (From Gradwohl Clinical Laboratory Methods and Diagnosis ed 4 1948 The C V Mosby Co)

disease be manifest (carrier state) or they may give rise to mild diarrhea lasting a short time If the infection is massive and virulent and the physical condition of the host unfavorable the intestine is invaded and the full blown disease begins The present belief is that it is the endotoxin released by disintegrating vibrios which is responsible for the destruction of the intestinal epithelium

With injury and desquamation of the epithelium, a serous effusion of prodigious amount pours into the lumen This is passed off as a diarrhea char

sion, but many patients are practically afebrile after the first day or two Often a rise in temperature precedes death, especially with uremia, and then quite high figures are seen We have no reason to believe that elevations were due to pyrogenic infusion fluids, in our time, as they may have been in the past The fact that little or no fever is often seen even when the patient's fluid balance has been restored reasonably well suggests that cholera is not an especially febrile disease, just as Napier (1943) declares Nor is it an especially "toxic" disease, as consideration of the symptoms will show, or a so called toxemia

COURSE OF THE DISEASE

Cholera progresses through well defined clinical stages, provided the patient survives each of them At any stage save that of incubation, he may succumb to the extreme results of fluid loss, but, enduring these, he may yet die of renal insufficiency If the temporary renal shutdown is not fatal, i e, if it does not exceed his tolerance, then recovery will follow and complications are relatively unimportant Uremia is hardly a "complication", it is a completely characteristic feature of cholera and a direct result of the essential disturbance of fluid balance The complications are pneumonia, keratitis (corneal ulcer), cholecystitis, parotitis, jaundice, and abortion

Incubation—This stage may occupy from 1 to 5 days usually 3 days, and may be characterized by vague abdominal distress and infrequently nausea and vomiting, but it is not usually certain that the patient accurately recalls these events It is probable that most patients have no symptoms during this stage If, however, the ingestion of vibrios took place long before the onset which was precipitated by intercurrent disease (e g, dysentery), then the incubation period must have been the duration of the carrier state, or a matter of weeks A very brief incubation period, perhaps only a few hours, is occasionally found during an epidemic, but its significance is difficult to determine

Evacuation—The diarrhea usually begins abruptly and with violence and is soon accompanied by profuse vomiting The stools are passed with a sense of relief, yet the patient is quickly prostrated, with retching, muscular cramps and occasionally hiccup Dehydration becomes obvious within a few hours and signs of circulatory embarrassment, together with *extreme thirst*, rapidly follow Depending on the body resources, evacuation may continue for only a few hours, or intermittently for as long as several days *During this time the picture of extreme shock develops* Exceptionally the onset may be progressive, with only a mild diarrhea and *feculent stools, but even then* within an hour or two, the stage of evacuation is in full course

Collapse—This is the stage of circulatory *failure*, called the "algid" stage, in which the patient lies prostrate, with rapid, weak, and later irregular pulse, distant heart sounds, extreme *hypotension* (*with a* systolic pressure of 60 mm or less, and frequently not determinable) and shallow, rapid respirations *Vomiting and retching cease, although diarrhea may* continue on a

gall bladder If the patient survives long enough this may show injury Organisms have been found in exudates from the lung in patients who later develop pneumonia This has given rise to debate whether septicemia exists particularly since vibrios are rarely detected in the circulating blood (Greig 1913 1914 1915 1916 Nichols 1916)

Post Mortem Findings

Post mortem findings reveal little more than is obvious during life extreme dehydration as reflected in the external appearance general tissues and serous membranes and some reaction about the lymphoid patches of the ileum It is customary to mention also the early rigor mortis and odd positions of the head and extremities When there has been renal involvement the tubules are markedly dilated and the lumen is filled with proteinaceous material there is some interstitial edema but the blood vessels are essentially normal



Fig 157 Kidney in Asiatic cholera Low power magnification (×150) (Courtesy of Oscar Felsenfeld) (From Gradwohl Clinical Laboratory Methods and Diagnosis ed 4 1948 The C V Mosby Co)

CLINICAL SYMPTOMS

The symptoms of cholera develop logically from the known disease processes and are peculiar only in respect to their unparalleled intensity What appear a multiplicity of signs and symptoms are the effects of damage to the intestinal mucosa (diarrhea and vomiting) extreme fluid loss medical shock (with the clinical picture of shock generally) and consequent circulatory failure and renal insufficiency (uremia) The origin and character of the several symptoms will be considered in detail

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Reaction—Now the peripheral circulation begins to return, and the skin feels warmer Diarrhea has ceased Although oliguria may be present, there is usually some irregular increase in the amount of the urine, with considerable albumin and casts The patient's color improves and the pulse is stronger Bile stained stools may be formed in small amounts, but more often nothing is passed If the patient can produce a liter of urine in 24 hours, it is assumed that recovery will follow

Renal Failure To reach the stage of reaction does not insure recovery This will depend on the re establishment of urinary secretion Even though the circulation returns azotemia may increase with hypertension, delirium convulsions and death in uremia

Sometimes the return of kidney function is intermittent, and finally unsuccessful As in other diseases with renal insufficiency, the blood pressure rises as if to bring about adequate filtration by force, in cholera, this will occur as well as the restored circulation can permit Some nitrogen is thus cleared, but the blood pressure may fall off again, and anuria may return See sawing of this kind may continue, and the patient may die or the quantity of urine may increase progressively albumin become a little less, and azotemia steadily diminish, until an ample flow of urine makes recovery a certainty We have witnessed the latter course during the administration of testosterone (Henderson et al, 1948) when clinical findings suggested irreparable kidney damage From 15 to 25 per cent of the deaths in cholera occur in uremia The proportion is larger in patients with damaged or overburdened kidneys (e g, pregnant women) Any measure which materially aids the restoration of renal function is of great practical value in cholera

The fact that some patients react well, and then go on to uremia has given rise to the supposition that as the circulation improves more toxin can be absorbed from the damaged intestine, and specific injury to the kidney is produced by this toxin On examination it will not be found that any lasting gain in renal function has been established and then lost On the contrary the patient is in renal failure from the stage of collapse, and only intermittently produces a little urine by the mechanism described, before dying eventually of uremia The case for a systemic action of cholera toxin is supported by some other findings but not so well by conditions involving the kidney

Convalescence This is usually rapid but the patient is long in a weakened condition and in early convalescence may collapse as a result of undue effort This is attributed to 'heart failure,' whatever the cause

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rapid thready and irregular pulse or a leaden complexion with labored shallow respirations ("asphyxial stage") or the advent of coma may portend the loss of the patient

Clinical Varieties Even in a single epidemic all grades of severity can be found The mild somewhat benign diarrheas ("cholerine") are limited to the early cases Patients with this so called choleraic diarrhea may remain ambulatory and never advance to the point of renal insufficiency They serve admirably as carriers

Cholera or "cholera gravis" is otherwise that disease which has been described differing from case to case only in the earliness of death and the predominant clinical features algid asphyctic typhoid uremic etc An interesting clinical variation is found in children where the picture of meningitis is commonly imitated

Cholera sicca (cholera siderans) is a rare form of cholera characterized by sudden collapse and death of a patient before there has even been any diarrhea Post mortem examination shows the presence of rice water containing cholera vibrios in the intestine Because of this perplexing phenomenon it is not possible to rule out a toxin as the cause of profound systemic disturbances in at least a few cases of cholera Whereas cholera sicca is said (Whitmore 1929) to occur in very old or severely debilitated subjects as after dengue or with pulmonary tuberculosis it is not limited to such patients Thus one may reflect on disturbances of salt and water balance severe enough to exceed the functional capacity of the adrenal cortex in any patient whose condition is extremely bad but in the case of robust individuals other explanations must be sought

LABORATORY FINDINGS

Serology

Agglutination produced by the patient's serum begins to appear on the fourth day of the disease in low titer (1 40) and reaches high values at about the seventh day (up to 1 1000) (Pasricha and Chatterjee 1939 Yacob and Chaudri 1945) The "H" antigen produces the more common and marked immune response The response is more or less specific for the infecting strain that is this is better agglutinated than the "standard" organism such as Inaba but exceptions occur Accompanying nonpathogenic vibrios may excite no serologic response whatever Because of the late development of serologic findings they are not of immediate diagnostic usefulness but they have confirmatory value and may be indispensable if vibrios have not been found in the stools *Agglutinins against Brucella* in titers of 1 500 may develop following vaccination against cholera (Eisele et al 1946)

Blood Characteristics

Leucocytosis is present in cholera The sedimentation rate is moderately increased (15 to 35 mm in 1 hour) The features of hemoconcentration are marked specific gravity 1 060 to 1 080 hematocrit 0 47 to 0 82 hemoglobin

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Depending on the material received, several procedures can be adopted

Abundant specimens can be plated directly on Aronson's medium and *V comma* taken off for agglutination at 18 hours, subculture should be made on plain or alkaline agar, however, to eliminate contaminants The D E C plate or Dieudonné's medium may be used and agglutination tested after 24 hours It is usual to inoculate an alkaline agar plate also directly from the specimen More scanty specimens should be first enriched by culture in alkaline peptone (pH 8 to 9) and vibrios taken off the surface after 4 to 8 hours for further culture Water should be cultured in 0 1 part of peptone with salt (peptone, 10 per cent, and sodium chloride, 5 per cent) for 24 hours in flasks and organisms taken off the surface At appropriate stages, a loopful of material is studied for form and motility

Agglutination Test Taking an organism in pure culture which shows the morphology and motility of *V comma*, agglutination is conclusive evidence of its identity (McLaughlin and Whitmore, 1910) A high titer anti O serum is used in serial dilutions up to 1 500 or 1 1,000 and a loopful taken for a hanging drop preparation Material from a plate colony *is mixed with it, and with an indifferent serum or saline in a control preparation, and the* two preparations compared for agglutination and for loss of motility

Immune serum can be prepared by inoculating a rabbit with a small number, half of a 2 mm loopful, of known *V comma*, suspended in saline and injected intravenously, and bleeding the animal after 8 days Such sera are also commercially available

Macroscopic agglutination (Strong, 1943) is carried out in a test tube, using a loopful of pure agar culture suspended in normal saline, 1 c c, to which is added 1 c c of saline containing the antiserum, and the mixture incubated for 2 hours The mixture is turbid to begin with but if complete agglutination has occurred it is perfectly clear and the organisms are found precipitated at the bottom of the tube Incomplete agglutination is seen as a residual turbidity, with some precipitation Agglutination should be complete at a serum dilution of 1 1000

Pfeiffer's phenomenon is an agglutination test which uses the peritoneal cavity of the guinea pig as the vessel and lysis of the vibrios as an end point It is reliable and rapid the peritoneal fluid being withdrawn after 15 to 20 minutes to determine whether the vibrios are nonmotile and deteriorated, if so, Pfeiffer's phenomenon is present, and the organisms are those for which the serum has activity

Culture of stools for *V comma* is made routinely as follows

1 Inoculate Dunham peptone water, incubate 8 hours
2 Make Gram stain, look for vibrios
3 Streak one of the following and incubate D F C plate, Dieudonné's medium Aronson's medium, alkaline agar plate, or other solid media
4 Isolate suspicious colonies
5 Agglutination with "O" antiserum
6 Hemolysis using 5 per cent sheep or goat cells

If there is no beta type hemolysis *the organism is V comma*, if beta hemolytic it is El Tor type

DIFFERENTIAL DIAGNOSIS

In any epidemic, when bacteriologic proof has been secured for prior cases (see above) an overwhelming gastroenteritis is automatically assumed to be cholera In isolated cases and indeed even in the presence of epidemic cholera it may be necessary to distinguish cases of exceptionally severe shigellosis and of "food poisoning," as well as some more unusual disorders such as malarial diarrhea, meningitis etc Not only is dysentery apt to co exist in cholera country, but there is great likelihood of cholera carriers being precipitated into clinical cholera by an intercurrent shigellosis etc , so that the diseases may co exist in the individual patient Fortunately, energetic treat

85 to 140 per cent erythrocytes up to 8 000 000 (Lebsenfeld 1938) The chemical abnormalities of dehydration acidosis and eventually azotemia are characteristic Blood phenol is reported to be elevated in relation to the severity of the disease The measurement of hemoconcentration can be carried out according to Scudder 1940 (See also Gradwohl 1948)

Bacteriologic Diagnosis

In the Field—With a common microscope and one stain such as carbol fuchsin vibrios can be recognized in the stool

A film composed of mucus shreds from the stool should be dried stained with carbol fuchsin 1 10 dilution dried and examined When cholera vibrios are present they appear as the characteristic comma bacillus and generally have the fish in stream appearance Such an examination does not of course distinguish *V comma* and nonpathogenic vibrios and it should be borne in mind that even in a cholera epidemic almost half the vibrios seen are not pathogens (Heiser 1914 Munson 1915) Identification must be made finally upon a stool sample or peptone water culture or even a tied loop of intestine sent to the laboratory If a high titer anticholera rabbit serum is available then agglutination can be tested with a bit of mucus from the stool (Dunbar 1913) An indifferent serum will not affect the motility of the vibrios while specific serum will cause motility to be lost If a clear difference is found between two specimens treated thus the test has real significance but if negative no conclusions should be drawn since a limited number of true *V comma* might respond to the test but be overlooked among other vibrios The occurrence of nonmotile *V comma* in some epidemics must also be remembered

In the Laboratory (Seneca) —Specimens should be sent with the least delay but if distances are great agar slants can be inoculated in the field and be found useful as long as 2 weeks afterward under tropical conditions (Whitmore 1929) or feces can be suspended in salt solution of 0.5 to 5 per cent strength (Pangamban and Schobl 1918) or in an equal part of bile for preserving the vibrios for several weeks

The laboratory diagnosis of cholera depends on agglutinating with specific serum the vibrios which have been grown in pure culture from a specimen To accomplish this it is necessary to cultivate V comma in a medium which prevents the growth of enteric organisms as well as possible such a medium almost always being very alkaline Prolific invention has been applied to such media which now include besides agar and peptone water Dieudonne alkaline blood agar Panja D E C medium (1943) or Aronson plate (1915) alkaline meat infusion agar (Goldberger 1913) bismuth sodium sulfite broth with brilliant green (Wilson and Blair 1931) or without the dye but buffered to high alkalinity (Read and Pandit 1941 Wilson and Reilly 1940) potassium tellurite (Gohar 1948a) starch egg medium with a striking combination of dyes (Wilson and Reilly 1940) a simple alkaline agar (Volpino 1916) and a great many others (Read et al 1941 Strong 1943) practically all of which serve very well (See Gradwohl 1948) The ideal medium one upon which only cholera vibrios will grow has yet to be discovered

actually under medical supervision about 20 to 30 per cent die the greater number in the stage *of collapse* and the remainder later of uremia but with intensive treatment administered under favorable hospital conditions the mortality may be less than 10 per cent It must be appreciated that patients who live long enough to reach the hospital are necessarily a selected group forming a small proportion of those involved in an epidemic The aged those with renal impairment and pregnant women are especially liable to uremia and as pregnant women usually abort there are the *considerable further risks* of sepsis Children have especially high mortality from cholera

The several clinical manifestations which influence individual prognosis have been mentioned in the clinical section (above)

TREATMENT

An extraordinary variety of supposedly therapeutic measures has come down through the history of cholera and many of these seem difficult to abandon however shadowy the evidence of benefit *More recent contributions* have no better standing even though their logic is more familiar and among these are potassium permanganate (to "oxidize" the "toxin") kaolin (to adsorb the same) and a variety of "disinfectants" With due respect to the honored history of these many objects it should be emphasized that *nothing* should be given the cholera patient *by mouth* unless there is excellent reason to believe it will influence the disease process *This does not however* leave an open field for the hypodermic injection of digitalis epinephrine etc the rationale for which can be debated

Intravenous saline is *the definitive and curative treatment of cholera* It should be given as early as possible and as frequently as necessary to preserve the volume of circulating blood as shown by the hematocrit or blood *specific gravity The blood pressure is a late sign for appraising blood volume* it falls only when no further compensation for a drastically reduced volume is possible and by this time it may be most difficult to restore the circulation even by energetic fluid therapy No rule should be set for the dosage of saline if repeated blood studies are practical the dosage is a *sufficient* amount (Latta 1831 1832) taking 1 060 as the highest permissible blood specific gravity and 50 as the highest hematocrit value If repeated determinations can not be done an empirical dosage of 2 000 c c for adults can be set for the outset of treatment to be repeated every 4 to 6 hours The dosage and interval can be modified according to the amount of fluid loss which is obvious in the individual patient If one administered a large excess *of saline* it would be possible to induce congestive heart failure the signs of which are dilatation of veins in the neck and presacral edema (in a recumbent patient) but as this *is not found during the treatment* of cholera it can be assumed that one is still short of restoring the lost fluid in average epidemic cases Hence the use of saline may be as liberal as desired Only patients with known cardiac pathology or those who pass from dehydration to congestion as a result of treatment call for special caution At the extreme are patients who have so

ment for cholera alone is appropriate to both diseases and in the circumstances of epidemic cholera the differentiation would seem academic

Dysentery due to Shigella or Salmonella may show mucus or blood in the stools but not fluid of the rice water character and there may be abdominal pain or cramps but not generalized muscular cramps involving the extremities anuria is not likely to occur The prolonged diarrhea of salmonellosis when it occurs may be markedly similar to cholera and has given rise to the expression cholera nostras for infections due to *S typhimurium* or *S enteritidis* A conclusive diagnosis must rest on bacteriologic study

Food poisoning can often be traced to its source involves a limited circle of patients and has an incubation period of 12 hours or less unusually short for cholera Knowing the source one might appraise whether it seems a likely medium for transmitting cholera But the clinical picture can be quite as cataclysmic as cholera itself and differentiation on these grounds may not be possible

Botulism is a prostrating disease due to the ingestion of the *Clostridium botulinum* toxin preformed in food It has an incubation period of several days with limited distribution It can be distinguished from cholera by the absence of rice water diarrhea and the development presently of central nervous symptoms (paralysis dysphagia diplopia aphonia)

Malaria prevails in much of the cholera country and may occur in a prostrating diarrheal form The stools are not rice water and the temperature is found high or cyclic A high temperature or splenomegaly should call for quick examination of a blood film and malaria may be found which demands immediate treatment If cholera is known to exist nearby the treatment should be instituted for *both* diseases

Poisoning with mushrooms arsenic mercury etc gives rise to more conspicuous vomiting than diarrhea and generally has a more limited local distribution than cholera If emesis is well established intensive saline therapy should be used on the assumption that cholera might *also* be present if known to be prevalent

PROGNOSIS

No one can accurately assess the absolute mortality due to cholera even within a single epidemic because of the uncertain proportion of the cases which are actually seen and diagnosed Under some conditions there may be one or there may be ten patients of whom no one knows for each one who is treated in part because of the uncertain communications present in the eastern world and in part because of the panic chaos and vast overwork of medical personnel that are present in cholera epidemic areas If therefore one speaks of 50 per cent mortality this includes some patients who have enjoyed medical cognizance and usually some treatment and others who have entered *into local statistics with uncertain accuracy as to both number* and diagnosis It is usually said that the average mortality is 50 per cent

Untreated cases are said to have 40 to 75 per cent mortality Of patients

Some fluid can be given by hypodermoclysis as well This is an auxiliary measure of no consequence in combating acute shock since the uptake of fluid from the tissues is slow at best Intraperitoneal injections are more difficult to give but act rapidly and well (Deb 1947) Finally fluids can be given by rectum if evacuation is not still in progress or has not yet begun (cholera sicca) (Goff and Denney, 1915)

Much emphasis has been given in the past to the use of alkaline infusions—made up with sodium bicarbonate (Rogers 1917) lactate (Banerjee 1936 Banerjee et al 1938 Hartmann 1929 Hartmann and Senn 1932) gluconate etc—in order to combat acidosis (Hartmann 1929 Hartmann and Senn 1932 Rogers 1916 Sellards 1917) It should be remembered that acidosis develops because of renal failure and despite the gratifying results that appear to attend the use of bicarbonate solutions it is not at all clear that correcting acidosis favorably influences renal function In all instances where this was thought to happen ample volumes of fluid had been restored to the general circulation which alone would have regained the acid base controlling function of the kidneys The practical objection to bicarbonate solutions is that they cannot be sterilized without decomposition to the hemolytic sodium carbonate the theoretical objection is that a great proportion of chloride lost from the digestive tract also needs to be replaced (Banerjee 1941) That sodium chloride can be given in excess does not seem likely

The custom of designating one type of infusion as most suitable for the stage of evacuation another for collapse still another if uremia threatens one especially adapted for controlling shock etc appears to ignore the single underlying disorder that gives rise to these successive manifestations It may be remarked that a sudden accession of fluid may be poorly handled by patients in collapse hence the first infusion must be administered slowly and with close observation and with particular notice of the temperature of the fluid When the response to saline infusions is limited it must be recalled that the advanced stages of diarrhea entail a loss of protein as well which can be made up by adding human plasma to the infusion if it is available There are otherwise no necessary departures from the intensive use of saline infusions as the central treatment of cholera

Sulfonamides—Since in any cholera epidemic up to 100 per cent of untreated patients will die while more than 90 per cent of patients treated with saline will survive it is difficult to appraise the effect of treatment directed against the vibrio itself It should also be remembered that the organism does not survive more than 3 to 5 days even if no drug is used so that treatment must have effect in the earliest course of the disease if it is to accomplish anything of use later it can only add to the embarrassment of the kidneys

Thus far there have been reports of the use of sulfaguanidine (Chopra et al 1941 Chu et al 1946 Gupta et al 1945, Huang 1944 Indian Research Fund Association Report 1943 1944 1946 Seal 1947), succinyl sulfathiazole (Indian Research Fund Association Report 1946), sulfadiazine

little remaining blood that the veins when cut down for instilling the infusion do not even bleed in such cases the requirement for fluid is so great that it may never be satisfied far less exceeded

The saline to be administered should ordinarily be physiologic salt solution 0 85 per cent NaCl pyrogen free in distilled water Hypertonic saline (13 75 Gm NaCl 0 25 Gm $CaCl_2$ per liter) is advised in "more severe" cases in fact it is difficult to distinguish which cholera patients are less severe than others or to show that one solution has served better than the other The same is true of improved solutions containing for example 5 per cent glucose (Gaertner 1915) These supply a modicum of nutrition (200 calories per liter!) which is of undoubted aid In actual practice one employs the materials at hand Even distilled water has been employed with apparent benefit (Sen Gupta 1945)

If there is actually any choice of solutions new information inclines one to the choice of a potassium containing infusion such as Rogers hypertonic mixture of NaCl 8 Gm $CaCl_2$ 0 25 Gm and KCl 0 4 Gm for the following reasons (1) As the patient recovers water is regained more quickly than electrolyte leaving the patient in a state analogous to salt depletion or water intoxication even though this fact is not apparent on clinical grounds Nominally at least an excess of salt is desirable from the time of collapse (2) Data from the treatment of infantile diarrheas in which fluid loss reaches somewhat the magnitude found in cholera suggest that one effect of a loss of extracellular fluid is movement of intracellular fluid outward to take its place in some measure As the latter contains primarily potassium there is a depletion of tissue potassium stores not remedied by the usual sodium salt infusions and adding subsequently to the general electrolyte derangement and systemic weakness Infusions providing a small proportion of potassium salts have in infants yielded considerably better results as judged clinically It is our belief that the same rationale applies in cholera As has been mentioned however it is not possible to distinguish on either clinical or statistical grounds whether one or another solution is the more appropriate hence the recommendation must be made on the basis of physiologic theory rather than conclusive experience

The solution should be warmed preferably to higher than the body temperature before administering Any convenient container partially filled with warm water and if possible surrounded by an insulating jacket for night or cold weather can be used to suspend the infusion bottle and keep its contents warm Whether an excessively warm infusion dilates the peripheral vessels and nullifies its own effectiveness in fitting the blood volume to the vascular bed may be disputed but certainly the temperature at the needle should never be less than 99° F and it ought to be 2 or [illegible] degrees higher in any except febrile patients The possibility of adjusting each patient's infusion to his body temperature at the time however attractive in theory is remote under the usual conditions of epidemic cholera

kaolin (Arneth, 1916, Kuhne, 1918), essential oils alcohol, atropine, irrigations of the stomach, acids by mouth, coffee to aid the kidneys, digitalis to aid the heart, Adrenalin, cupping, hot packs mustard plasters etc More recently we hear of bacteriophage (Jadin 1936, Pasricha, 1942, Sen and Basu 1945), antitoxic serum, antivibrio serum, drugs such as Atabrine (Panja 1945), dyes such as brilliant green (Panja and Ghosh, 1943), antibiotics such as streptomycin (Reimann et al, 1946), etc *It is seldom reported that any of these measures has failed to produce marked benefit in a goodly series of cases especially since all are treated with saline infusions and have an excellent chance to recover for that reason*

The use of chloramphenicol (Chloromycetin) in experimental cholera infection has been reported by Gauld et al (1949) Gauld and fellow workers attempted to determine the activity of this drug against *V comma* both in *vitro and in the treatment of mice experimentally inoculated with this organism* Chloromycetin was tested for its inhibitory effect upon two strains of *V comma cultured in single strength brain heart infusion broth with a pH of* 7 6 Complete inhibition of growth was obtained with 0 005 mg of Chloromycetin per cubic centimeter of culture media *In vivo experiments* were made with Chloromycetin Each experiment included groups of mice that were inoculated with *V comma* and treated with sulfadiazine Cultures of the Inaba and the Ogawa strains of *V comma* on veal infusion broth were used to induce the experimental disease in mice In each instance 0 5 c c of inoculum suspended in 5 per cent hog gastric mucin was injected intraperitoneally While it is not possible to reproduce the human disease in laboratory animals the *intraperitoneal injection of large doses of V comma* into mice causes a rapidly developing septicemia and peritonitis lacking however, the vomiting diarrhea and extreme dehydration characteristic of cholera in man The *important conclusions* from this work were that Chloromycetin is an effective antibiotic for the treatment of mice experimentally *inoculated with V comma,* when given in adequate doses between 1 hour before and 2 hours after the injection of the *organisms These experiments suggest* the possible usefulness of the drug as a chemoprophylactic agent among human contacts of cholera

Editor's note (O T) *Recently* bacitracin, neomycin and terramycin have proved useful in experimental cholera

Testosterone—We (*Henderson et al* 1948) have administered large doses of testosterone propionate to cholera patients who were in uremia less as a therapeutic measure than as a study in experimental medicine, the object being to utilize the restorative function known to be exerted upon the injured kidney by androgenic hormones (The supporting data, being rather extensive, are presented in full in our report) The resulting *decline in* mortality was sufficiently obvious to confer a therapeutic status to the experiment In 27 *uremic* patients the mortality was *less than 20 per cent* as compared with 70 per cent usually found under the same circumstances in the same epidemic We employed 25 or *50 mg testosterone* propionate daily by intramuscular injection, an essentially arbitrary amount, there is no objection

(Chu and Huang 1946, and Chu et al, 1946 Indian Research Fund Association Report Reimann et al, 1946), a modified sulfathiazole (Bhatnagar et al, 1948) and various other sulfonamides (Lehiri 1945, Pasricha 1942, Sadusk and Oswald 1946, Sen and Basu, 1945) Only one drastic experiment (Indian Research Fund Association Report 1946) used the drug without saline, in 53 cases, with a mortality of 21 per cent compared with 75 per cent in 44 control patients This certainly furnishes proof of the theoretical value of anti infective therapy, but its practical significance must be doubted since any patient receiving medical attention at all can equally well receive saline, when the mortality is even lower The difference produced by sulfonamides among saline treated patients is less manifest with sulfaguanidine the mortality is reduced from 6 to 2 per cent (Indian Research Fund Association Report 1946) or from 5 to 1 per cent (Gupta et al 1945) or in a smaller series from 39 to 17 per cent (Indian Research Fund Association Report 1946) with sulfadiazine from 10 to 0 per cent (Chu and Huang 1946) Thus taking all the experience together, it can be said that the best modern treatment is apt to produce a mortality of 6 per cent while the further addition of sulfonamides will reduce this to only 3 per cent (Seneca and Henderson) Yet the inclusion of a few more or less favorable cases in a series or the difference of a day's time in starting treatment may lead adventitiously to greater contrasts than this

A choice of sulfonamides is easily made All who have tropical experience look with dread upon compounds like sulfadiazine an absorbable sulfonamide having a likelihood to precipitate in the kidney if the patient is at all dehydrated (and even if he is not) Regardless of its activity against the cholera vibrio sulfadiazine is not a drug of choice in the tropics, and very particularly not in the fluid depletion of cholera Instead one should elect one of the nonsystemic or unabsorbable" compounds In view of irregularities of its behavior sulfaguanidine is not an ideal member of this class The choice lies between succinylsulfathiazole and phthalyl sulfacetimide and of these phthalyl sulfacetimide is known to have not only excellent vibriocidal power but a striking ability to become absorbed into the proper tissue of the intestine—rather than so to speak accumulate within the lumen where it can affect the free noninvading organisms only Our own experience (Seneca and Henderson) in a preliminary series of 40 cases was quite satisfactory Only one patient was lost and no toxic action of any kind could be attributed to phthalyl sulfacetimide If therefore the means are at hand to supplement the established fluid therapy of cholera with sulfonamides the use of phthalyl sulfacetimide is especially to be recommended Failing this succinylsulfathiazole should be of some value Other compounds including some recent innovations for which the evidence is unimpressive are better dispensed with rather than add further injury with doubtful benefit

Other Methods—It would be tedious to enumerate the preparations which have no recognizable value in cholera but enjoy earnest support in various parts of the world From olden times we have purgatives permanganate

must be suspected. Water in wells can be treated according to the local fashion with either potassium permanganate or calcium hypochlorite in order to produce a residual chlorine content of 2 ppm or higher. (Convenient testing devices can be used to show whether the residue is sufficient. If the taste is obnoxious the water can be allowed to stand for a day if protected from contamination or a little ammonia can be added before chlorination.) Since there is not universal agreement upon the security given by these measures it is likely that more water will be boiled as the epidemic becomes more oppressive. The inclination toward tea drinking in cholera country has probably saved countless European lives.

Contaminated water can be found on the hands as well as the food, especially if one is dealing with cholera patients. Personal cleanliness is urgently needed.

In the presence of an actual case of cholera, continuous disinfection of the patient's dejecta and of linen and other articles in contact with the patient must be carried out. There must be no opportunity for patients or carriers to contaminate the water supplies (or food) with their feces. Flies must be dealt with by screening and by insecticide sprays used indoors, and their bodies must be treated as infected material.

Most of these efforts are self evident. One must have full cognizance of the infectious material discharged by patients and carriers and where it goes. One must have full knowledge of what comes into the mouth and where it comes from. Trained personnel are aware of both, indifferent native personnel may pay little attention to either.

On a more than local scale the importation of cholera into a new region or country can be guarded against by quarantine, a delay allowing incubating cholera to become manifest (Smith 1938), but carriers can be detected only by repeated stool examinations and remain an important hazard. It is said (Strong 1943), however, that epidemic cholera has not been transmitted by a carrier of more than 2 months standing. Air travel has introduced a new complexity, since the incubation period of cholera may not elapse en route as it necessarily does in sea travel, and thus rules have been placed in effect to delay the arrival of persons from cholera country until incubation can be completed. In the end, of course, the control of the disease depends above all upon the security of water supplies in the country of arrival. That this is never perfect has been vividly shown, for example, by amebiasis in Chicago, and may at any time become apparent again.

Immunization.—The use of vibrio material as an inoculation material was introduced as early as 1885 by Ferran, who employed living organisms injected subcutaneously. At present a variety of methods is used to prepare vaccine (Jennings and Linton 1944, Pandit 1948, Ranta and Dolman 1943, Sokhey 1944) and various tests such as the guinea pig (Sugino 1935) and mouse protection tests (appraising the antibodies developed in the human subject's serum) are carried out in the effort to evaluate the materials used (Ciuca and Balteanu, 1926, Griffitts 1944, Ranta and Dolman 1944). In

to much larger doses Our impression was that renal function was more rapidly (and more usually) restored in the treated patients, and in typical cases it was possible to trace a relationship between the treatment and this effect although only an extended series could show this conclusively Not a large number of cholera patients nowdays die in uremia but of deaths in cholera uremia is responsible for a very large proportion. We have felt that our experiment should be continued wherever the circumstances permit While the beneficial effect of testosterone is mainly related to kidney function it should not be overlooked that it also produces sodium chloride and water retention which is probably responsible for part of the physiologic benefit It is known that the adrenocortical hormone administered as desoxycorticosterone acetate has even more marked action and aids in maintaining the blood pressure under adverse conditions of water balance It might well be found that both hormones can be used to advantage prophylactically if the opportunity is presented rather than permit uremia to develop Moreover when utilized sufficiently long in advance of collapse the use of testosterone may contribute greatly to improved nitrogen balance

General Management—The cholera patient should be put at rest and disturbed as little as possible Morphine should be administered to relieve anxiety restlessness and muscular cramps the dosage should not be calculated to reduce the diarrhea as this is futile No food can usually be given by mouth as it will be vomited immediately Every effort should be made to induce the patient to take fluids by mouth Many cannot take fluids but one must keep trying to get fluids into these patients Where water or fruit juice cannot be tolerated try shaved ice a spoonful at a time or better still shaved ice with ginger ale Some control of the vomiting can be secured with small doses of cocaine such as 8 mg ($\frac{1}{8}$ gr) and it may be advantageous to administer this dropwise under the tongue in smaller amounts Intravenous fluids should be started as soon as the diagnosis is made and should be continued If phthalyl sulfacetimide is available 5 Gm should be given as early as possible then 1 Gm every 2 hours for 5 days by mouth

When the stage of collapse is reached other medication should be withheld but the infusions maintained perhaps with the addition of glucose 5 per cent and thiamine (2 mg per liter of glucose solution) Glycosuria can be ignored If testosterone propionate is used it can be begun at any time but preferably before renal insufficiency is advanced unless one is making a deliberate selection of cases and at least 50 mg should be administered daily

PROPHYLAXIS

Control of Transmission—When cholera is known to exist in a region utmost attention must be paid to the sterilization of water—not only drinking water which can be observed and controlled but also the water which contaminates vegetables sea food etc For this reason eating uncooked food is dangerous Even fruits before being peeled should be washed clean in boiled water or steeped in boiling water Ice and all contents of an ice refrigerator

health activity in China It would be a happy and novel event if the cholera vibrio, transmitted as freely as before, never found a human intestine in which it could survive and multiply

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ulations are usually subcutaneous (but they may also be intradermal—nja and Das, 1947) and consist of 8 000 million killed *V comma* per cubic timeter, the dosage being 0 5, 0 5, and 1 0 c c at intervals of 7 to 10 days various criteria, the induced immunity is short, lasting only 6 months or less, that reinjection of 1 c c is practiced every 4 months in the presence of demic cholera While the older literature contains a diversity of opinion to the effectiveness of vaccination, and indeed it might be impossible to show clusively that it is effective, experience strongly favors it In India, for ample cholera is ten times as common among unvaccinated as among vaccinated persons, using either a phenolized or a "protein free" material (Pandit 18, Sokhey, 1944) A similar reduction of morbidity was reported in the eek army (Arnaud, 1914) and in other armies (Kersten, 1918) The Nizam Hyderabad forbade pilgrims to cross his territory unless they were vaccinated ainst cholera when it was found that the disease was practically eradicated m their groups (*palkies*) even though it had been present when they started ao, 1947) Though morbidity may occur even with vaccination, the mortality demonstrably smaller We did not see patients with cholera who had been en complete vaccination 3 weeks or more previously while those who had en inoculated more recently were indistinguishable from other patients is not necessary to use a vaccine prepared from numerous strains of cholera brio The Ogawa and Inaba types should be present and recently isolated ains probably have greater protective value than stock organisms

Recently a cholera toxoid obtained from El Tor vibrios (Gohar, 1948c, kita 1939), has been employed, it has been combined with killed vibrios d administered simultaneously with vaccine of dysentery bacilli a rational d desirable combination (Felsenfeld and Young 1945)

Despite the probable value of vaccination, the most important factor to otect against cholera is general and personal hygiene

Chemoprophylaxis—Bacterial inoculation, while statistically effective, sures variable protection to the individual and then only after a delay of veral weeks. It is evident that greater security can be secured for persons ose to an actual epidemic This has been attempted by giving prophylactic ses of sulfadiazine (Peterson 1946), but it is our belief that a less toxic lfonamide is desirable for routine use in large groups of people We have licated (Seneca and Henderson) that such a compound as phthalyl lfacetimide can be used for this purpose It is applicable to routine adminis ation on a large scale without immediate supervision since no detectable ood concentration is set up and there is no conceivable hazard of crystalluria ontrolled groups such as military personnel or hospital staffs exposed to olera in a region can be afforded continuous protection from the first day a standardized prophylactic dose such as 1 Gm daily Whether such a nple measure will ever find province or nation wide application, as in India, problematic although the far more troublesome vaccination has been extended groups as exten

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TABLE XVII NOMENCLATURE OF SALMONELLAE AND SHIGELLAE

PRESENT SCIENTIFIC NAME	SYNONYMS
Salmonella typhi	*Eberthella typhosa* *Salmonella typhosa* *Bacillus typhosus* *Bacterium typhosum* Typhoid bacillus
Salmonella paratyphi A	*Salmonella paratyphi* *Bacillus paratyphosus A* *Bacterium paratyphosum A* Paratyphoid A bacillus
Salmonella paratyphi B	*Salmonella schottmuelleri* *Bacillus paratyphosus B* *Bacterium paratyphosum B* Paratyphoid B bacillus
Salmonella paratyphi C	*Salmonella hirschfeldii* *Bacillus paratyphosus C* *Bacterium paratyphosum C* Van Loghem's bacillus Paratyphoid C bacillus
Salmonella typhimurium	*Salmonella enteritidis* Breslau *Salmonella aertrycke* *Bacillus pestis caviae* *Bacterium typhi murium* *Bacillus aertrycke* *Bacillus breslau*
Salmonella choleraesuis	*Salmonella suipestifer* *Bacillus suipestifer* *Bacterium suipestifer* Hog cholera bacillus
Salmonella enteritidis	*Salmonella enteritidis* Gaertner *Bacillus enteritidis* *Bacillus enteritidis* Gaertner *Bacterium enteritidis* *Bacterium enteritidis* Gaertner *Bacillus gaertner*
Shigella dysenteriae	*Shigella dysenteriae* (Shiga) *Bacterium dysenteriae* Shiga Shiga Kruse bacillus
Shigella ambigua	*Shigella ambigua* Schmitz *Bacterium dysenteriae* "Schmitz" Schmitz bacillus
Shigella paradysenteriae	*Shigella paradysenteriae* Flexner *Shigella paradysenteriae* Flexner Boyd *Bacterium dysenteriae* Flexner Flexner bacillus
Shigella alkalescens	*Bacterium alkalescens*
Shigella sonnei	*Shigella dysenteriae* Sonne *Shigella dispar** *Bacterium dysenteriae* Sonne *Bacterium dysenteriae* Sonne Kruse Sonne bacillus Sonne Kruse bacillus Sonne Duval bacillus
Shigella dispar	*Shigella dispar* Castellani

*Often confused with *Shigella dispar* Castellani

CHAPTER 29

SALMONELLOSIS—SHIGELLOSIS

Oscar Felsenfeld and Viola Mae Young

SALMONELLOSIS

(Typhoid and Paratyphoid, Salmonella Infections, Enteric Fever)

DEFINITION

Salmonellosis is a disease or carrier state caused by bacteria belonging to the genus Salmonella

ETIOLOGY

The members of the genus Salmonella are usually characterized as gram negative non spore forming, mostly motile aerobic and facultative anaerobic microorganisms which ferment dextrose and mannitol with the formation of acid and gas (with the exception of the typhoid bacillus, the fowl cholera organism and a few so-called anaerogenic strains which produce acid only but no gas) do not ferment sucrose lactose or salicin do not form indole or acetylmethylcarbinol and which have a serologic pattern which fits into the White Kauffmann Edwards schema All Salmonellae are pathogenic for man and animals

The genus was named for Salmon who first described an organism belonging to this group (*S choleraesuis*) Some bacteria previously placed into different genera have now been definitely added to the Salmonella group the typhoid bacillus (*S typhi* or *S typhosa*) and the fowl cholera organism (*S gallinarum*) Some difficulties have been experienced with the nomenclature of Salmonellae

In spite of the efforts of the Salmonella centers obsolete and unaccepted nomenclature is frequently used Table XVII shows the most frequently used terms

The isolation of Salmonellae is described in Chapter 71 Here we wish only to reemphasize that the exact diagnosis of the type is a task which must be carried out in specially equipped laboratories, called Salmonella centers It is recommended however that the local laboratory test the basic biological properties of every organism suspected of being a Salmonella eventually perform an agglutination test with a polyvalent serum and report to the physician "Salmonella present Type to follow"

Details regarding the typing of Salmonellae are contained in the publications of Kauffmann (1941) Edwards and Bruner (1943 Monteverde (1943) Felsenfeld (1947) and Cruickshank (1948)

About 150 types and varieties of Salmonella are known to date While any of them might be encountered in a given case or outbreak of salmonellosis but 15 strains comprise the majority of types isolated from man

EPIDEMIOLOGY

To Hormaeche et al (1940) belongs credit for the so called "Montevideo Doctrine" which asserts that persons contracting Salmonella infections react

In America where large quantities of fowl and eggs are consum Salmonellae which occur in fowl are frequently found in human salmonello Hinshaw et al (1944) and Kessel et al (1945) first emphasized this fact T meat of poultry, eggs, and egg products may carry the infection

Meat of hogs and cows very often contain Salmonellae Rubin et (1942), Cherry et al (1943), Hormaeche et al (1940), and others have fou Salmonellae even in the best, federally inspected market meat Brain lym nodes, and liver seem to be the most frequent sites of Salmonellae in anim The animals may be symptomless carriers

Rodents frequently harbor Salmonellae without dying of the infectio Rats and mice may contaminate stored food with their droppings and th transmit the infectious agent to man

Flies are recognized vectors of salmonellosis They carry the organis passively on their wings or legs also in stool particles

Certain foods provide an excellent medium for the growth of Salmonell Nearly all milk and egg products as cream, mayonnaise and ice cream a capable of supporting multiplication or survival of these organisms S monellae survive on vegetables kept in the icebox for many weeks (Felsenfe and Young 1945)

The duration of the carrier state is variable Rubinstein et al (194 found that about 2 per cent of all persons infected with Salmonellae excre these organisms for a period longer than 1 year

For the enumeration of the sources of infection and carrier state, refe ence is made to the articles of Bornstein (1943), Felsenfeld (1945), a Gradwohl (1948) Only the epidemiology and distribution of the most co mon Salmonella strains will be discussed in this chapter

S typhosa the typhoid bacillus, causes only human infection mostly in the form typhoid fever The organism is transferred from man to man chiefly by carriers who act food handlers, and by polluted water It occurs throughout the world but is a particula serious problem in neglected rural communities with little or no sewage disposal or food a water sanitation The average mortality is 8 per cent Many epidemics of typhoid fever m be traced with the aid of bacteriophage typing of the causative organism According to t phage susceptibility, several subtypes of *S typhosa* are known

S paratyphi A predominates in subtropical and tropical regions It is also present continental Europe This infection follows the typical man to man pattern It is natur that food and water soiled with excreta of both active cases and of carriers play an emine role in the communication of paratyphoid A infections

S paratyphi B causes about 20 per cent of the salmonellosis cases in America. It usually communicated by man but has frequently been recovered from pigs, cows, sheep, a rats, chiefly in South America It is present all over the world, being superseded, howeve in some areas by the more numerous paratyphoid A infections *

S paratyphi C is practically unknown in America but it is frequent in the Near Ea India, and Netherlands Indies Its epidemiology resembles that of *S paratyphi A*

S typhimurium is the most common Salmonella, causing about 30 to 35 per cent of a Salmonella infections It usually produces an enteritis of a few days' duration *S typh*

*In recent years *S paratyphi B* has been encountered less frequently

in different manners depending on several factors among which age and general health play a great role Thus septicemia and meningitis are more frequent in young animals and in infants than in healthy adults Similarly higher mortality is observed in debilitated people The strain of the organism is of lesser importance for the course of the disease This doctrine has been generally accepted chiefly after statistical proof by Edwards and Bruner (1943) Pornstein (1943) Seligmann et al (1946), and Hinshaw et al (1944) invalidated the Kieler Doctrine ' which gave credit only to the strain of Salmonella in the determination of the course of the infection

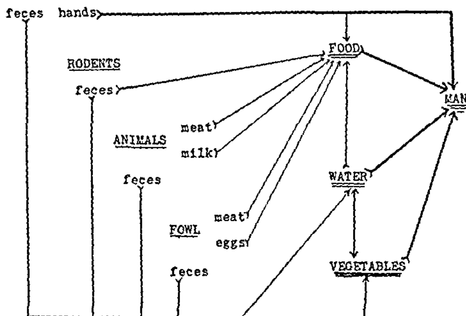


Fig 158.—The transmission of Salmonella

Certain Salmonellae as *S typhosa S paratyphi* A and C are mostly transferred from man to man Patients during the actual illness are not such dangerous sources of infection as are symptomless carriers Salmonellae transmitted from man to man are most frequently transferred by dejecta which adhere to the fingers of food handlers and by drinking water which has been soiled with fecal material The supervision of food handlers including dairy workers is an important measure for the prevention of salmonellosis The story of Typhoid Mary is so well known that it need not be repeated here Not only *are those Salmonellae which like the typhoid bacillus are common to man but* not animals propagated by food handlers but other Salmonellae are also frequently spread by human beings

The Classical Enteric Fever

In most instances classical enteric fever is a separate well defined clinical entity with typical pathologic findings It is described in more detail in Chapter 30

Classical enteric fever is a disease of the lymphatic tissues of the intestine spleen and bone marrow and is characterized by the invasion of these organs by large mononuclear phagocytes also called ' typhoid cells ' The initial hyperplasia may dissolve through resorption or focal necrosis may develop chiefly when vascular occlusions caused by bacterial emboli enter into the picture

The invasion by large mononuclears causes hyperplasia of the Peyer s patches and solitary lymph follicles These lymphatic structures become enlarged and project above the surface of the intestine The changes are most evident in the lower part of the ileum and are difficult to follow in the large intestine because of the less extensive lymph follicles in that part of the bowel. After swelling necrosis follows Round oval or elongated ulcers result which due to the topography of the Peyer's patches extend along the longitudinal axis of the intestine When only a part of the lymphatic structure necrotizes irregular ulcers result

The ulcers have a relatively clean floor They reach into the muscularis but may be so deep that they extend to the peritoneum Edema is usually observed in the environment of the ulcers

These changes either are resorbed or they heal practically without any scar formation Perforations develop in certain instances

The abdominal lymphatics are congested and enlarged due to the invasion by large mononuclears The spleen is acutely congested and enlarged it is deep red and soft The sinuses are distended There are many red blood cells in the pulp Large mononuclear cells are very numerous small areas of necrosis are not infrequent The bone marrow shows many large mononuclear cells and necrotic foci The liver is large swollen and cloudy There is a proliferation of the mononuclear cells and focal necrosis usually causing small lesions The gall bladder shows only slight inflammation as a rule The kidneys do not reveal much pathology cloudy swelling is often observed.

The heart muscle may suffer degenerative changes brown atrophy is frequently observed in fatal cases The femoral and saphenous veins and the cerebral sinuses are often thrombosed The lungs may suffer from pneumotyphoid caused by Salmonellae in which typical organisms are isolated from the sputum Secondary bronchitis and bronchopneumonia seem to be more frequent than the lobular typhoid pneumonia

The bones chiefly the tibia sternum ribs and spine may be the seats of chronic suppurative lesions The rose spots of the skin are caused by bacillary emboli of the capillaries

It is self evident that the quantity and extension of these lesions may vary from case to case

murium is spread by man, hogs rodents, cows, and fowl *Human carriers, meat of infected animals and fowl, eggs, and food contaminated by rodents are the chief sources of human disease*

S choleraesuis occurs throughout the world Most infections are observed in America, England and the Pacific area Pork is the principal source of infection Human carriers are extremely rare This organism is the most dangerous of the Salmonellae, causing septicemia, with a mortality of about 25 per cent

S derby is found *under* all climes but attains local importance only in America The *chief sources* of infection are man fowl and hogs Sick poultry *seems to* play the greatest role *S derby* usually causes only enteritis

S thompson is rare in America but *frequent* in Europe where it attacks man and *poultry* Few cases have been reported from the tropics Most infections originate from eggs

S montevideo is found most *frequently in* the New World and in the Mediterranean area Man, fowl and hogs harbor this organism In human beings *enteritis is* the most common clinical manifestation

S oranienburg occurs more *frequently* in *Europe* than does *S montevideo* It has the same epidemiologic features

S newport has a world wide distribution acquiring much local importance *in* the warmer parts of America, in India, and in the Pacific area Man poultry, and hogs are the principal sources of infection *The* disease appears under various clinical pictures of salmonellosis

S enteritidis is a major cause of salmonellosis in *Europe India* and the Pacific area but is only a minor agent in America *being infrequent* in American fowl

S dublin is practically unknown in North America but is very often encountered *in* South America South Africa Australia, and England It is endemic *in cattle S dublin* infection of ducks in Denmark is the probable cause of *its frequency* in human beings in that *country*

S panama is a typical organism of the New World It is often isolated from man poultry and pigs causing in *human beings* every clinical form of salmonellosis

S anatum is frequent in America the Mediterranean area and Netherlands Indies It is readily isolated from man poultry and hogs *The* disease usually caused by *S anatum* is enteritis

Other Salmonellae, which are more unusual may attain local importance *but these are of less frequency* The strains enumerated above cause 90 per cent of the world s Salmonella infections To complete the list the following Salmonellae may be mentioned

S saint paul, S reading S abortusbovis *S* bredeney *S* bareilly *S hartford S tennessee, S muenchen S berta S* sendai *S* pullorum *S gallinarum S london S give, S meleagridis S* newington *S new brunswick S senftenberg S pretoria S worthington, S kentucky S minnesota* and *S urbana*

Because *of the* infrequent occurrence of these Salmonellae any statement regarding their means of communication would be merely theorizing without adequate foundation

PATHOLOGY

The post mortem findings differ in most cases according to the clinical form of salmonellosis Deviations from this rule however are frequent Extensive changes with few clinical symptoms and vice versa, are by no means rare exceptions There is little connection between the causative organism and the pathologic changes except in a few instances such as in the classic picture presented by typhoid fever *S choleraesuis* infections etc In the following paragraphs the classification of salmonellosis according to Hormaeche et al (1940) is followed with regard to Manson Bahr s (1945) observations

stood however that salmonellosis may cause a true appendicitis but the pseudoappendiceal picture is more frequent

Hormaeche et al (1940) divide Salmonella gastroenteritis in children into a dysenteric and a choleriform group The pathologic findings however are only exceptionally characteristic There may be hyperemia and inflammation If ulceration is present the ulcers are very often small In many cases they are limited to the large intestine In some cases an acute gastritis is present (Angrist and Mollow 1946) Sometimes the lesions reach the rectosigmoid and resemble bacillary dysentery

The lesions heal without scar formation or give rise to sequelae such as mucous colitis irritable colon " or ulcerative colitis

Pseudosurgical Syndrome

Pseudosurgical syndrome is a clinical picture rather than a pathologic entity It was most extensively studied by Seligmann et al (1944 1946) Salmonella enteritis may appear under the clinical picture of appendicitis cholecystitis or inflammations of the female genital organs The pathologic changes are rarely typical and the diagnosis is made by laboratory examinations

Carrier State

Persons who excrete Salmonellae without being actually ill are called Salmonella carriers Such a state may develop after an attack of salmonellosis and the patient is then called a ' convalescent carrier ' The contact carrier acquired his infection during an outbreak without becoming sick The chronic carrier excretes Salmonellae for a considerable length of time e g for more than one year The active carrier harbors the organisms in his intestinal canal while the 'passive carrier discharges them only during the period of ingestion

The most outstanding pathologic changes are found in chronic carriers The gall bladder usually shows only a slight inflammation in enteric fever In most carriers however the gall bladder contains numerous lymphatic nests and infiltrates Whether Salmonellae can predispose to the formation of gall stones or whether gall stones favor the settlement of Salmonellae is open to discussion Extirpation of the gall bladder has cured numerous carriers this practice is much recommended by many authorities

CLINICAL SYMPTOMS

The clinical symptoms as related to statistics on the occurrence of Salmonellae are discussed by Edwards and Bruner (1943) Rubinstein et al (1944) Seligmann et al (1946) Varela and Zozaya from Mexico (1942) Vaccaro et al from Chile (1943) Kitching from Canada (1945) Bruner (1945) and Maccolini (1941) from the Mediterranean area Hayes and Freeman from India (1945) Lindberg and Bayliss from the Pacific area (1946) they are described in the survey articles of Hormaeche et al (1940), Bornstein

Typhoid Like Fever (Salmonella Fever)

As stated before although any Salmonella may cause this symptom complex, the principal agents are the paratyphoid bacilli *S sendai*, *S panama*, and others The pathology has been much discussed Recent contributions, such as that of Angrist and Mollov (1946) shed much light upon the pathology of this form of salmonellosis

Autopsy findings in Salmonella fever show wide variations The picture of classical typhoid (enteric) fever is not infrequent in fatal cases More often however specific post mortem changes are lacking Little or no pathology is present in the lymphatic tissues Inflammation may dominate the picture, without much hyperplasia The participation of organs other than the intestine may be less than in the classical enteric fever The lungs and bones are rarely affected Venous thrombi are only exceptionally found Perforations are infrequent The spleen is not always enlarged Emboli of the skin capillaries are rare except in paratyphoid B fever The gall bladder is often attacked

Septicemia

There is a bacteriemia in all cases of classical enteric fever and in Salmonella fever A separate clinical entity called Salmonella septicemia includes a symptom complex in which the septic high remittent fever predominates Little or no changes are found in the intestines If such alterations are present they may be typhoidal in nature or only a nonspecific inflammation is seen When the case is examined at autopsy the initial intestinal disturbances which frequently introduce Salmonella septicemia are already healed in the great majority of fatalities Frequently however the infection enters the blood stream through the tonsils without passing through the intestines In such instances the participation of the intestinal lymphatic apparatus is not necessarily greater than that of the other parts of the body Bronchitis and bronchopneumonia are the most frequent collateral findings

Salmonella septicemia may lead to diseases of various organs Meningitis parametritis cholecystitis endocarditis pneumonia pyelitis nephritis and osteomyelitis are the most frequent forms of inflammation and abscess formation Meningitis and osteomyelitis are more common in infants while pneumonia pyelonephritis and cholecystitis occur more frequently in old people

Salmonella septicemia seems to be far more common in young children and in persons suffering from other diseases—arteriosclerosis, diabetes nephritis and leucemia—than in healthy adults Thus the autopsy findings are obscured by the pathology which must be attributed to the wasting disease which lowered the resistance of the patient to such an extent that the development of the septicemia became possible

Enteritis

Salmonella enteritis (or gastroenteritis) rarely is a direct cause of death Death is somewhat more frequently observed when salmonellosis causes a pseudoappendiceal syndrome upon which surgery is performed It is under-

Headache malaise insomnia apathy and dizziness are regular features of the picture Pain in the back and in the limbs is often reported Anorexia is usually present stupor develops in about 75 per cent and delirium in about 30 per cent of the cases Psychosis is rare

While a stiff neck is present in about 10 per cent of the patients meningismus and meningitis are not very frequent These must be differentiated by cerebrospinal fluid examination

The tongue is coated its margins are often clean thus presenting the picture of the typhoid V The mouth is dry and thirst is a frequent complaint The cheeks are flushed giving the patient the well known facies typhica

An early symptom is epistaxis which is observed in about 25 per cent of the patients Respiratory catarrhs are very frequent being present in about 50 per cent of the cases The number of cases with bronchitis increases during the later course of the disease While coryza is very frequent bronchitis develops in about 75 per cent pneumonia in about 10 per cent of the cases Bronchopneumonia and pneumonia usually develop during the third week or later

The pulse is slow principally before the temperature reaches its maximum The pulse rate is slower than one would expect from the temperature rarely exceeding 96 to 120 per minute at 103° to 105° F A dicrotic pulse is present in about 40 per cent of the patients This dicrotism is mostly observed during the second and third week of the disease The blood pressure is usually low A soft systolic blowing sound is present in about 30 per cent of the cases it is not of organic nature Endocarditis myocarditis and pericarditis are very rare Thrombophlebitis is a complication in about 5 per cent of the patients it develops usually on the legs with an insidious onset Thrombophlebitis rarely occurs before the third week of the illness

Less than 50 per cent of the patients have diarrhea Pea soup stools are present in about 30 per cent of the cases Only about 10 per cent of the patients have diarrhea in the beginning of the disease and severe diarrhea does not develop in more than 20 per cent of the cases Constipation follows the diarrhea and may be very obstinate

Foul breath and sordes are frequent Herpes labialis is only exceptionally seen Nausea and vomiting occur in about 40 per cent of the patients

The abdomen is usually distended and tender upon pressure An enlarged liver may be felt in about 25 per cent of the cases usually after the temperature assumes the continual character The spleen is increased in size it becomes palpable at the end of the first week in about 75 per cent of the patients in other instances later It is not excessively enlarged The organ is tender and soft Spleen enlargement may persist during the entire course of the disease or for only a few weeks or days

Cholecystitis and jaundice occur in about 5 per cent of the cases

Other organ involvements such as cystitis pyelitis neuritis conjunctivitis arthritis osteomyelitis and otitis are not too frequent

(1943) and Felsenfeld (1945) To these basic forms must be added the "classical enteric fever" of Manson Bahr (1945) as well as the pseudosurgical syndrome emphasized by Seligmann et al (1944, 1946) The great importance of the different course of salmonellosis in children is pointed out by Hormaeche et al (1940 1943) As has been emphasized Salmonella infections tend to produce a graver disease in young children The classical typhoid fever, however, often has a light course in this age group due to the greater tendency to resorption of the intestinal infiltrations and lesser tendency to vascular occlusions of the relatively wide intestinal capillaries in children

The clinical forms of salmonellosis will be discussed according to the already enumerated types of this disease

Classical Enteric Fever

This disease is decreasing in the United States (1946) The number of observed cases decreased during the past years to one fifth of its former height The classical picture as described by Manson Bahr (1945) is not too often observed today because of the use of vaccination sulfonamide medication and antibiotics The latter drugs are often applied during the beginning of the disease when it is mistaken for a pulmonary illness dysentery meningitis or sepsis

The incubation period is 3 to 21 days seldom shorter or longer

The course of the classical typhoid type follows the well known pattern characterized by increase of the body temperature during the first week continuous fever during the second and third weeks followed by lysis during the fourth and fifth weeks This fever curve however may be shorter or longer in any of its parts Much material regarding the typical typhoid fever has been collected and published by Manson Bahr (1945) Ganguli and Zeug (1945) and Stuart and Pullen (1946)

According to these descriptions and personal observations the classical typhoid fever begins with a gradually rising temperature or in about 10 per cent of the cases it begins suddenly A sudden onset may be accompanied by chills or rigor These initial chills must be distinguished from the transient chills which occur in many typhoid patients during the later course of the disease In most instances the initial elevations of temperature are not observed by the physician because patients only rarely are seen during the first days of the disease

The temperature reaches 102° to 105° F during the peak of the febrile stage While during the first week (ascending phase) the daily variations of the temperature do not exceed 1° to 1.5° F in the second and third weeks (continuous fever) the difference between maximum and minimum temperatures may be between 1° and 5° F Remitting temperatures begin usually during the third week but often occur as early as the second week The lysis extends for 1 to 2 weeks with marked remissions Thus the entire febrile period lasts 4 to 6 weeks While the classical temperature curve is preserved the fever may last from 3 to 15 weeks

Pharyngitis and bronchitis are more common in typhoid infections than in salmonellosis caused by other organisms

On the whole the clinical picture of typhoid like fever is not characteristic The diagnosis cannot be *made solely by physical examination and* observation

Septicemia

The prodromal stadium may begin with diarrhea which usually disappears during the later course of the disease In such cases the stools are light colored or green and contain mucus

The septicemia proper frequently begins with chills followed by the stage of diarrhea *either immediately or several days later In many instances no* bowel disturbances are present at all and the only symptom is fever In a small number of cases the beginning is insidious with slowly rising temperatures

The fever is remittent There are great differences between the morning *and the evening thermometer readings 5° F or more Continuous fever may* be present for some days but its general character remains remittent The duration of the febrile episode is irregular 3 to 6 weeks may be considered average

There is malaise headache pain in the back and in the limbs anorexia and *thirst Delirium may be present Insomnia and apathy are frequent* The tongue is heavily coated and the mouth is dry

The pulse is soft and usually accelerated A dicrotic pulse is not often observed

Abdominal distention and pain may be present but often there is no intestinal *discomfort The spleen is usually enlarged soft and tender*

Rose spots are very rarely seen

Bronchitis is often the most outstanding symptom and may dominate the clinical picture to such an extent that only the diagnosis of bronchitis or bronchopneumonia is made

Salmonella septicemia is often observed in newborn babies and in older persons in the latter case usually superimposed upon a wasting sickness as *arteriosclerosis diabetes* tuberculosis leucemia nephritis or malaria The presence of these diseases may stand so strongly in the foreground that the possibility of a superimposed salmonellosis is not considered especially in the absence of diarrhea

Salmonella septicemia frequently leads to localized affections In children meningitis is the most frequent and most feared localization Salmonella meningitis in children was extensively studied by Neter (1944) who called attention to the necessity of considering Salmonellae as a possible cause in every case of meningitis *The clinical picture of Salmonella meningitis does* not show symptoms which permit its differentiation from acute meningitis caused by other nonacid fast organisms

Cholangitis cholecystitis pleuritis pericarditis thrombophlebitis osteomyelitis and pelvic inflammations often occur during or after Salmonella

Rose spots (roseola typhosa) occur during the second week, less frequently during the first or third week in about 30 per cent of the patients These spots are pale slightly raised macular, round oval or slightly irregular, about 2 to 5 mm in diameter varying considerably in shape and size and disappearing upon pressure There may be few or many roseolae distributed on the abdomen chest and extremities most often on the trunk The face is rarely involved The soles the palms and the scalp do not become involved The spots do not itch Roseola appears in crops lasting for 2 to 6 days

Among the other skin affections occurring in typhoid fever furuncles decubiti and other ulcerations are the sign of uncleanliness insufficient nursing care and circulatory weakness

Relapses of typhoid fever are not rare they are observed in about 15 per cent of the cases They develop 3 to 40 days after the termination of the typical fever curve and last for 1 to 6 weeks They are more frequent in patients treated with antibiotics

Typhoid Like Fever (Salmonella Fever)

In the tropics Salmonella fever is frequently caused by Salmonellae other than the typhoid bacillus In persons who have been immunized against typhoid fever the classical picture of typhoid is rarely observed The disease very often takes the course of Salmonella fever While children suffer more often from grave forms of salmonellosis a mild course of typhoid is not rare in them The fever however usually reaches a far higher peak than in adults

Salmonella fever differs from the classical typhoid fever by generally having a shorter duration Cases with a prolonged course however have also been observed The fever rarely exceeds 104° F

The disease may begin suddenly with a chill though an insidious onset is far more common Anorexia headache and malaise are frequent symptoms The tongue is usually coated The patient does not have the characteristic toxic appearance of a person suffering from classical typhoid fever

Epistaxis may occur Labial herpes has also been described

There is no discrepancy between the temperature and the pulse rate in most cases

Abdominal pain is usually intense There is distention and often meteorism The spleen may or may not be enlarged The meteorism particularly in children does not always permit palpation of this organ

Rose spots are frequently observed in the tropics in paratyphoid B fever but are usually absent in other Salmonella infections

Diarrhea may be entirely absent Constipation throughout the entire course of the disease is often experienced in children On the other hand profuse diarrhea beginning during the first or second week of the disease is not uncommon

A pseudosurgical syndrome assuming the picture of an appendicitis cholecystitis or pelvic inflammation is often present.

ent state will reveal vague symptoms which may be attributed to the gall bladder or to the kidneys Many carriers are accustomed to abdominal discomfort and do not complain about them

COMPLICATIONS AND SEQUELAE

Any clinical form of salmonellosis may give rise to complications or sequelae

Perforations

Perforations are the most feared complications in typhoid fever Perforations occur during the period of intestinal ulcerations in about 2 to 5 per cent of the typhoid cases

The beginning is usually sudden Tenderness and rigidity of the abdomen develop within a very short time Hiccup is frequently present Collapse occurs very often During the later course symptoms of peritonitis develop

Hemorrhages

It is often difficult to draw the line between "normal" bleeding from typhoid ulcers and hemorrhage An alarming hemorrhage consists of the expulsion of tarry *stools* or even pure blood without a considerable admixture *of fecal material Hemorrhages* from the higher parts of the small intestine may cause hematemesis Such intensive bleeding is observed *as often as in about 10 per cent of the patients in the tropics There may be only one large* hemorrhage or the bleeding may be repeated The amount of blood varies considerably in each case

Respiratory Disorders

Bronchitis is not uncommon in salmonellosis Pneumonia or bronchopneumonia develops in about 10 per cent of the cases of typhoid fever and Salmonella septicemia Salmonellae may be present in the sputum or the lung involvement may be caused by secondary invaders

Manson Bahr (1945) calls attention to the possible activation of tuberculosis during salmonellosis and suggests that pulmonary tuberculosis be *considered in every case of prolonged* bronchitis or bronchopneumonia during typhoid fever The author noted that in cases of pulmonary tuberculosis the *clinical condition* became worse due to *Salmonella paratyphi B* infections in a children s hospital

Pleuritis occurs in about 3 per cent of the cases Empyema is rare

Circulatory Disturbances

Thrombophlebitis is observed in typhoid fever and in *Salmonella septicemia It* is usually a late complication and the beginning is insidious The legs are *most frequently involved* Thrombophlebitis may cause embolism with all its sequelae

Endocarditis myocarditis and pericarditis are rather rare They are observed in less than 1 per cent of Salmonella infections The myocardial involvement is often demonstrated only with the aid of electrocardiography

septicemia An abscess may develop in nearly any part of the human body following such an infection

There is very little in the clinical picture of Salmonella septicemia that would permit the diagnosis of this disease solely on the ground of physical examination and observation

Enteritis

The incubation time of Salmonella enteritis varies from 8 hours to 2 weeks

The fever has nothing in common with the curve observed in typhoid In most cases there is no fever at all About 40 per cent of the patients have low grade fever lasting from 2 to 4 days The temperature seldom exceeds 102° F Exceptionally chills high fever and prostration with quickly fatal ending are observed usually in otherwise sick debilitated persons

The onset is sudden in 90 per cent of the cases There is diarrhea similar to bacillary dysentery The number of stools varies from 2 to 20 a day The stools contain much mucus but usually no blood

There is abdominal distention pain and meteorism The pain may be localized in the appendiceal gall bladder pelvic or rectosigmoidal region It must be kept in mind that true Salmonella appendicitis cholecystitis and salpingitis do exist and therefore these symptoms must be evaluated carefully Dicrotic pulse or an acutely enlarged spleen is very rarely seen

There is usually little toxicity Headache and malaise may be present Rose spots are not observed Bronchitis is rare Vomiting is a frequent symptom chiefly in the beginning of the disease

The proctoscopic examination reveals in about 30 per cent of the cases an inflamed intestine similar to that observed in mild bacillary dysentery

Syndromic Salmonellosis

As previously stated salmonellosis may occur under the picture of appendicitis cholecystitis or pelvic inflammation Such symptoms may be due to acute pathology of the intestines in the neighborhood of the appendix gall bladder or pelvic organs On the other hand Salmonellae may attack these organs The differential diagnosis is made by clinical examination and laboratory investigation

In the tropics salmonellosis often occurs in a malarial or relapsing fever type when the fever falls for a few days and rises again after such intervals According to the length of the periods between the attacks a malarial or a relapsing fever like curve may be observed

The dengue like or influenza like type of typhoid is characterized by high fever of short duration involvement of the respiratory organs and critical fall of temperature

Carrier State

As a general rule no symptoms are observed in chronic carriers In several instances however thorough examination of the history and of the pres

It must be pointed out that the skin of persons living in the rural tropics often suffers from bacterial and mycotic lesions as well as *from bites of arthropods* Rose spots must therefore be evaluated carefully Furunculosis is not rare in hot regions during febrile salmonellosis

Intestinal Tract

As a rule lesions in the intestinal tract heal without scar formation In some cases however chronic nonspecific colitis has been observed as a sequela of Salmonella enterocolitis Salmonellae have also been recovered from spastic colitis (irritable colon) mucous colitis and regional ileitis While an irritable colon or ulcerative colitis is less frequently observed after salmonellosis than in connection with a Shigella *Endamoeba histolytica* or streptococcal infection *the role of Salmonellae in regional ileitis is a matter which* merits further attention We have isolated Salmonellae from 2 (out of 6) cases of regional ileitis the organisms were identified as *S typhimurium* and *S montevideo* respectively

LABORATORY DIAGNOSIS

Isolation of Salmonellae

The methods recommended for the isolation of Salmonellae from feces and urine are described in Chapter 71

One must keep in mind that several repeated stool examinations are necessary to recover the causative agent Both stools and urine must be investigated

In the classical typhoid fever in Salmonella fever and septicemia the organisms are cultured from the blood stream and from the bone marrow with relative ease Methods recommended for such cultures are described in Gradwohl *Clinical Laboratory Methods and Diagnosis* ed 4 1948 pp 156a 157b In this chapter we wish only to point out that best results are obtained when every blood sample is inoculated simultaneously into three media brain heart infusion with p amino benzoic acid agar and penicillinase fluid thioglycollate medium and trypticase soy broth Salmonellae grow in the first and last of these liquids *If gram negative rods are seen in smears* from these culture fluids blood and tryptose agar plates are streaked from *them* Salmonella colonies which grow well under aerobic and anaerobic conditions and in a carbon dioxide atmosphere are identified by the usual procedure

It must be kept in mind that blood and bone marrow cultures are positive for Salmonellae more often during the first period of the disease than during the later weeks

Agglutination Reactions

The most frequent types of agglutination tests performed in salmonellosis are

The Tube Agglutination Test (Widal Reaction) —This test is carried out by preparing serial dilutions of the patient s serum from 1 10 to 1 2560 and adding suspensions of Salmonellae to each *dilution*

Decubiti develop in patients with circulatory disturbances and in persons lacking proper nursing care

Cholangitis and Cholecystitis

These are more frequent complications and sequelae of salmonellosis than is generally known About 5 per cent of all Salmonella infections show a low grade cholecystitis and more than 25 per cent reveal an impaired liver function when tested with sensitivity reactions e g the cephalin cholesterol flocculation test

Pathologic changes in the gall bladder are often found in so called healthy chronic carriers of Salmonellae

Nervous System Disturbances

Meningitis is frequent in small children Neuritis is infrequent but has been described as a sequela in typhoid and paratyphoid infections

Meningismus is not rare It can be differentiated from meningitis by laboratory examination

Genitourinary Lesions

Salpingitis, parametritis or perimetritis has been observed in about 1 per cent of female patients suffering from salmonellosis Salmonella endometritis seems to be rare The symptoms do not differ from those caused by other pyogenic organisms

Pyelitis and pyelonephritis belong among the less common Salmonella infections Involvement of the urinary system caused by secondary invaders is not rare in typhoid fever typhoid like fever and Salmonella septicemia While the organisms are excreted through the urine in about 25 per cent of febrile salmonellosis lesions of the kidneys or the urinary bladder due to Salmonellae themselves are infrequent

Pregnant women often miscarry during febrile salmonellosis Enteritis however is easily tolerated during gestation

Locomotor Apparatus

Salmonella arthritis belongs among the rarities Osteomyelitis chiefly in children is more frequently observed Typhoid bacilli *S typhimurium* and *S paratyphi B* are the chief offenders The ribs the spine and the bones of the extremities are the most frequent seats of suppurative lesions which show very little tendency to spontaneous healing

Abscess Formation and Skin Lesions

Salmonellae chiefly those which cause septicemia may cause localized suppurative lesions in the form of abscesses of the skin of the brain or of the internal secretory glands Pus in the pleural and abdominal cavities may contain Salmonellae

Atrophic skin lesions may occur and alopecia often develops after typhoid fever

Hematology

Anemia is not rare in salmonellosis Cases with fever show most commonly a decrease in the number of red blood cells and of hemoglobin The lowest findings are frequently recorded during the third or fourth week of the disease

A slight increase in the number of white blood cells is not unusual in the earliest days of salmonellosis 8 000 to 11 000 leucocytes per cubic millimeter are frequently counted during this period

Leucopenia is the rule during the later course of febrile salmonellosis There is a decrease in the polymorphonuclear cells with a relative increase in the mononuclears The number of white blood cells returns to normal by the end of the sickness

The leucopenia is caused by the leucotoxin the presence of which has been proved in a number of Salmonella cultures

Perforations of the intestine suppurative processes secondary infections and other similar conditions may cause leucocytosis

Urinalysis

Urinalysis frequently reveals the presence of protein during the first part of febrile salmonellosis Casts are observed in a small percentage of the cases

The diazo reaction is frequently positive in febrile salmonellosis Reports are lacking on large scale examinations in cases suffering only from Salmonella enteritis

PROGNOSIS

The over all mortality of salmonellosis is 5 to 6 per cent The fatality rate differs according to the age group and the clinical form of salmonellosis In America the death rate of classical typhoid fever varies between 10 and 15 per cent in children from 5 to 10 per cent in old people from 25 to 35 per cent The mortality of Salmonella fever is 5 to 10 per cent in children 10 to 15 per cent in old people 15 to 20 per cent The fatality of Salmonella septicemia is 15 to 20 per cent in children 40 to 60 per cent in old people 30 to 70 per cent Enteritis kills 1 to 3 per cent of the patients *

DIFFERENTIAL DIAGNOSIS

Sepsis may be differentiated by the result of blood cultures It is essential that no sulfonamides and no antibiotics be given to the patient before the blood is drawn

Miliary tuberculosis is often difficult to differentiate from febrile salmonellosis Frequent cultures of blood stools and urine for Salmonellae ophthalmoscopic examination x ray pictures of the chest and in many cases the rose spots will determine the diagnosis

*Recent antibiotics have greatly reduced these mortality rates.

The Slide Agglutination Test (Spot Agglutination Test) —This reaction was devised by Welch and Stuart (1936) Small decreasing amounts of the patient's serum are placed with a Kahn pipette into excavations of a glass plate Three hundredths amounts of a heavy suspension of Salmonellae are added to each drop of serum and the results are read after a few minutes

The Whole Blood Test —The whole blood test was described by Prumpt (1940) A drop of freshly collected or dry blood is mixed with 1 drop of antigen which contains sodium citrate Agglutination developing within 1 minute is considered significant and equivalent to a positive Widal test with at least a 1 80 dilution of the serum

The Vi Agglutination Test —The technic and significance of the Vi agglutination test have been discussed by Prower (1944) Soman (1945) and Gunther (1946) (Gradwohl *Clinical Laboratory Methods and Diagnosis* ed 4 1948 p 1468) This test is helpful in detecting typhoid carriers On the other hand it is positive in a fairly large number of uninfected persons

After vaccination or previous attacks of salmonellosis and in diseases caused by agents other than Salmonella (malaria pyelitis etc) sera often give positive agglutination tests On the other hand Salmonella infections which involve only the intestinal tract and even Salmonella fever due to certain strains (as *S paratyphi A*) do not show an increased agglutination titer

Frequently gross incongruities have been observed between the strain isolated from the patient and the result of the agglutination tests The antigens commonly used for the serologic detection of salmonellosis in America are prepared from the typhoid bacillus and from *S paratyphi A* and *S paratyphi B* while the great majority of salmonelloses are caused by other organisms (Bornstein 1943 Seligmann et al 1946 Felsenfeld 1945) When the usual antigens are tested an amazing maze of negative and positive findings results There are many cross reactions between Salmonellae It is recommended therefore that polyvalent antigens be used Bornstein (1943) and Felsenfeld (1947) devised such agglutinogens A positive reaction with these antigens indicates only that the patient has Salmonella antibodies

The difficulties described above warrant a cautious evaluation of agglutination tests in salmonellosis It must be kept in mind that negative results are not only possible but frequent and that positive agglutination tests may be due to other causes The following procedure is therefore recommended

The agglutination test should be employed first in the beginning of the disease It must be repeated 1 week to 10 days later Significance must be attributed only to high titer (1 80 or more) reactions both with O and H antigens and to agglutination tests which upon repetition show at least a four fold increase of one or both of the agglutination titers

Recently developed excellent culture methods for the detection of Salmonellae from the patient reduce the importance of serologic tests

Sulfonamide Drugs

Kolmer and Rule (1941) and Lawrence and Sprague (1941) found sulfonamides slightly effective in vitro and in animal experiments with Salmonellae. Hardy (1943) was able to reduce temporarily the number of excreted typhoid bacilli by sulfonamide medication. Hutner and Zahl (1942), Rachmilewitz and Braun (1943), and others found that sulfonamide drugs reduced the toxicity of Salmonellae. Most authors, however, are very skeptical about the use of sulfonamide preparations in salmonellosis.

We have seen but little influence of sulfonamides upon salmonellosis except in the reduction of toxic symptoms. The fever curve may be altered and the organisms are more difficult to isolate from the patient during sulfonamide treatment. The use of such drugs, therefore, is recommended only in septic cases and in carriers after gall bladder removal (Manson-Bahr, 1943).*

Antibiotics

Thomas and Levine (1945) and Riser et al. (1946) studied the action of penicillin upon Salmonellae. Penicillin caused the appearance of involution forms of typhoid bacilli. Different strains showed varying susceptibility to penicillin. About 10 units per c.c. were necessary to prevent the multiplication of typhoid bacilli.

According to our experiments, the susceptibility of Salmonellae to antibiotics shows great variations. In most cases of salmonellosis the only result of penicillin and streptomycin medication is that it impairs the effectiveness of *laboratory diagnostic methods.*

Bigger (1946), McSweeney (1946) and Comerford et al. (1946) found that penicillin and sulfathiazole given simultaneously act synergetically upon cases and carriers of typhoid fever. This method of treatment deserves further trial. In vitro experiments show that combinations of soluble sulfonamide drugs and antibiotics (penicillin and streptomycin) have a very favorable action upon Salmonellae. Shwartzman (1945) was able to improve the action of penicillin by *adding to it methionine, threonine and methionine sulfoxide.*

Streptomycin has been regarded as a most promising antibiotic. It was first tested in vitro and in animals by Schatz et al. (1944), Jones et al. (1944) and West et al. (1945). Extensive experiments in human salmonellosis were carried out by Elias and Durso (1945) and Reimann et al. (1945).

The dose of streptomycin is 1 to 4 million units per day, given per os or injected. In our experience 4 million units daily are necessary *for the* average case. It is important to keep in mind that the susceptibility of Salmonella strains to this antibiotic varies greatly. Unwanted reactions from the liver, skin, and other organs are frequent. The treatment must be carried out for a long time, at least 4 days after the symptoms have disappeared. Because of its collateral action, streptomycin should be reserved for serious cases of salmonellosis and supported by sulfonamides. Daily doses of 2 to 4 Gm. of

*See also Chapters 64 and 65.

Typhus shows a rapid pulse se in the white blood cells, and a typical eruption

Malaria and relapsing fever l by the examination of blood smears The consistency and s in malaria are different in many instances

Beginning meningitis may l l t typhoid fever and vice versa The type of vomiting the rigidity k which develops during the third to fifth day, and Kernig s symp t l t the proper diagnosis It must be kept in mind however that S ll n lla meningitis is not as rare as generally thought Many cases of S ll ell meningitis are diagnosed as "influenza meningitis' when the diff tiation is based solely upon the finding of ' gram negative pleomorphic r ls resembling influenza bacilli" in the smears from the spinal fluid Such rganisms are often proved in culture as Salmonellae

Brucellosis has its own immunology and bacteriology The brucellergin test the opsonocytophagic index and in many cases, the specific agglutination and blood culture will help to establish the diagnosis of an attack of brucellosis resembling Salmonella fever

Appendicitis differs from Salmonella pseudoappendicitis by the increase in white blood cells It must be remembered however that an initial slight leucocytosis is not rare in salmonellosis The true appendicitis caused by Salmonella cannot be differentiated from appendicitis evoked by other factors

Tuberculous peritonitis in children may cause numerous differential diagnostic difficulties Laboratory examination gives proper leads for the diagnosis

Gastroenteritis caused by Staphylococci differs from Salmonella infections by the shorter period of incubation lack of fever preponderance of vomiting abdominal cramps diarrhea and prostration

Streptococcus gastroenteritis is usually mild with nausea abdominal pain and diarrhea

The last two diseases as well as atypical cases of cholera and bacillary dysentery can be differentiated only by the isolation of a Salmonella Shigella or Vibrio from the patient or of the cocci from the incriminated food

TREATMENT

Specific Serum

Serotherapy is recommended in classical typhoid fever Felix produced a serum which proved promising in animal experiments and in clinical trials Felix s serum is given in 25 c c doses on 3 successive days during the early course of the disease The serum reduces the toxic symptoms Serotherapy during the later course of Salmonellosis is valueless

Sera against other Salmonellae are not available Their use would be restricted to septic cases

The diet must be supplemented with vitamins preferably in injections Fifty to 100 mg thiamine hydrochloride 500 to 1 000 mg ascorbic acid and 1 to 2 mg vitamin K must be injected daily If infusions or transfusions are given these substances are dissolved in the fluid Folic acid may be added

Specific Chemotherapy

Reiter and Marburg (1943) recommended the use of tin stearate and colloidal metallic tin Twenty 0 012 Gm tablets are given the first day 10 tablets per day during the subsequent 9 days

Kleeberg (1941 1945) advocates the use of mandelic acid in typhoid Severe diabetes peptic ulcer and nephritis are contraindications for this treatment *Good results have been observed in mild cases*

Clark et al (1945) observed excellent results with gentian violet in animals infected with Salmonellae This method may also find use in human medicine

Constipation and Diarrhea

Cathartics must never be given in constipation A tepid saline enema will bring prompt action without endangering the patient

Diarrhea was considered a symptom worthy of suppression by many authorities of the European Continent Large amounts of kaolin and animal charcoal were given About the latter Thomayer (1919) reporting on a long series of typhoid cases remarked It colors the stools black I have not observed any other effect of this medication

It is customary to give absorbents in Salmonella enteritis Kaolin alone or in combination with magnesium is the drug of choice

Against abdominal discomfort during Salmonella enteritis combinations of papaverine and belladonna occasionally with a small addition of a barbiturate may be used In most cases however one does not find it necessary to employ such medication

Complications

Oral hygiene is of utmost importance A cold cream can be used to treat the lips

Bronchitis bronchopneumonia and pneumonia are treated according to the rules of the management of such diseases Ipecac (ipecacuanha) however is often badly tolerated and codeine may increase the constipation

When an intestinal perforation occurs an operation must be contemplated Whole blood 250 to 500 c c or 500 to 1 000 c c of plasma are given daily Glucose infusions are also indicated Generous doses of streptomycin and penicillin should be given together with sulfaguanidine sulfasuxidine or sulfaphthalidine

In cases of hemorrhage morphine or Pantopon is injected Most authorities recommend refraining from the use of opium Large transfusions

sulfapyridine sulfathiazole sulfadiazine or phthalyl sulfacetimide given with an equal amount of sodium bicarbonate are recommended for this purpose Sulfonamide medication is possible however only when the urinary output can be maintained at a high level

As this book goes to press two new antibiotics aureomycin and Chloromycetin have been introduced in the treatment of salmonellosis Experiments have shown that these drugs are more effective in salmonellosis than is streptomycin Dihydrostreptomycin a detoxicated form of streptomycin has also been introduced *

Vaccine Therapy

Vaccine therapy favored so much in the past has few adherents at present Magrou and Brison (1945) recommended it using alcoholized vaccines

Transfusions

As Dewar (1946) pointed out convalescent whole blood has a beneficial action upon typhoid fever Even when convalescent blood is not available whole blood in doses of 500 c c is strongly indicated in hemorrhages

Plasma has proved very beneficial in toxic cases About 250 to 500 c c should be given daily

In dehydration when blood products are not available infusions with 5 per cent glucose are recommended 2 to 4 liters are given daily Plasma injections may be combined with glucose infusions

Hydrotherapy

When the temperature is higher than 102° F washing with water at 20° to 25° C 3 or 4 times a day with a sponge is recommended Some aromatic spirits or vinegar may be added to the water

An ice bag may be applied to the head when the patient s condition indicates it

Dietary Treatment

The ancient starvation diet is no longer used in typhoid fever A diet consisting of 4 000 to 5 000 calories is given The protein intake must not fall below 75 Gm Manson Bahr (1945) calls attention to the necessity of selecting for the patient such food from the dietary list that he likes

The fluid intake must be 4 to 6 liters a day Fruit juices weak tea or coffee and soups will make up most of this amount To increase the calorie value lactose or sucrose should be added to the fluids

Meat broth and cream soups are recommended Milk is best tolerated in the form of custards chocolate and malted milk Four to 8 eggs are recommended each day Butter is given frequently

Toast crackers mashed potatoes well cooked rice tapioca strained cereals farina Jello puddings and oranges complete the diet

No food is given during intestinal bleeding

* At the time of proofreading neomycin and polymyxin D as well as [illegible] have also proved beneficial in salmonellosis

4 Sanitary Water Supply

Wherever wholesome and safe water has been secured *typhoid fever has* decreased or even disappeared If well protected natural sources are not available filtration chlorination or the simple but very effective method of *boiling will produce good water*

5 Proper Sewage Disposal

Protection of the community from fecal infection can be accomplished only by instituting proper rules for the disposal of fecal and urinary material Education of the population is the first step to be taken to accomplish this measure Septic tanks and properly operating sewage systems are the most effective measures against intestinal infections Where not even septic tanks can be installed the borehole latrine should be tried

6 Other Sanitary Measures

Shellfish have *often been proved to convey salmonellosis Control of* shellfish is therefore essential

Flies may transfer Salmonellae passively from feces to food Control of flies is necessary for any successful antienteric program

Fomites such as books used by salmonellosis patients easily transfer the infection Disinfection is essential

7 Protective Immunization

The most commonly used vaccine consists of 1 000 million typhoid bacilli and 750 millions each of *S paratyphi A* and *B* per c c At weekly or 10 day intervals 0 5 1 0 and 1 0 c c is injected under the skin If revaccination is necessary 0 1 c c of the vaccine is injected under the skin This vaccine is the T A B vaccine The past war years brought much progress in its composition and application The typhoid organism used in the T A B vaccine was *the Rawlings strain* which was substituted by the Foxill #58 strain isolated from a carrier in Panama

Much attention is being paid to the importance of the Vi antigen in typhoid vaccination Such a vaccine was devised by Felix *It contains in each* c c 1 000 million typhoid Vi and 500 millions of each *S paratyphi A B* and *C* organisms Two tenths to 0 25 c c is injected first After 3 weeks 0 4 to 0 5 c c is given

Luippold and Longfellow (1942 1943 1946) proved in a long series of experiments that there is some cross protection between typhoid and paratyphoid B organisms while *S paratyphi A* does not show cross protection with any of these Salmonellae They found too that the T A B vaccine protects against the organisms from which it is prepared against *S enteritidis* and against *S typhimurium* but not against *S choleraesuis* and *S oranienburg* It has also been proved that the Vi antigen from *S ballerup* or *E coli* 5396 protects against

500 to 1,000 c c of whole blood, are indicated No food is given per os for few days when weak tea and milk with lactose or sucrose may be tried Manson Bahr (1945) recommends 2 to 4 mg vitamin K daily, and twice a da an enema with 1 liter of tepid saline During the later course of the diseas the amount of food is slowly increased until the full Salmonella diet is given

Other complications are treated according to the rules of medical or sur gical therapy applied to pyogenic infections

Carriers

Carriers may often be cured by gall bladder extirpation In some states e g Massachusetts this procedure is officially recommended Sulfonamid treatment is indicated after the operation

PROPHYLAXIS

The general rules for prevention of salmonellosis can be summarized as

1 Search for Human Carriers

Every person who has had salmonellosis should be subjected to repeated stool and urine examinations After febrile salmonellosis the bile should also be examined for Salmonellae

2 Eradication of Animal Disease

Fowl hogs and cows are known carriers of salmonellosis Flocks o birds should be protected against Salmonella infections by enforcing quaran tine rules and vaccination Carriers are frequent among animals the meat o which is used for human consumption Such animals do not necessarily show gross pathologic changes except by thorough inspection Extensive bac teriologic surveys are therefore needed to clear these foci of infection

3 Protection of Food

Protection From Human Carriers—Only persons known not to harbor Salmonellae Shigellae or *Endamoeba histolytica* should be permitted to handle food Food handlers should be subjected to periodic examinations

Destruction of Salmonellae in Infected Foods—Meat and milk of infected animals and meat and eggs of infected birds often contain Salmonellae Pas teurization of the milk is a satisfactory measure for destroying Salmonellae Unfortunately eggs and meat are not often brought to a sufficiently high tem perature during cooking to destroy Salmonellae in the inside portions of the meat puddings and other products

Proper Storage of Food—Rodents are often infected with Salmonellae and may contaminate food during storage if they have access to it

Proper Cleaning of Vegetables Eaten Raw—Vegetables fertilized with human or animal excreta or contaminated by fowl fecal material may carry Salmonellae Proper washing and cooking will destroy these organisms

4 Sanitary Water Supply

Wherever wholesome and safe water has been secured typhoid fever has decreased or even disappeared If well protected natural sources are not available filtration chlorination or the simple but very effective method of boiling will produce good water

5 Proper Sewage Disposal

Protection of the community from fecal infection can be accomplished only by instituting proper rules for the disposal of fecal and urinary material Education of the population is the first step to be taken to accomplish this measure Septic tanks and properly operating sewage systems are the most effective measures against intestinal infections Where not even septic tanks can be installed *the borehole latrine should be tried*

6 Other Sanitary Measures

Shellfish have often been proved to convey salmonellosis Control of shellfish is therefore essential

Flies may transfer Salmonellae passively from feces to food Control of flies is necessary for any successful antienteric program

Fomites such as books used by salmonellosis patients *easily transfer the* infection Disinfection is essential

7 Protective Immunization

The most commonly used vaccine consists of 1 000 million typhoid bacilli and 750 millions each of *S paratyphi A* and *B* per c c At weekly or 10 day intervals 0 5 1 0 and 1 0 c c is injected under the skin If revaccination is *necessary 0 1 c c of the vaccine is injected under the skin* This vaccine is the T A B vaccine The past war years brought much progress in its composition and application The typhoid organism used in the T A B vaccine was the Rawlings strain which was substituted by the "Povill #58" strain isolated from a carrier in Panama

Much attention is being paid to the importance of the Vi antigen in typhoid vaccination *Such a vaccine was devised by Felix It contains in each c c 1 000 million typhoid Vi and 500 millions of each S paratyphi A B* and *C* organisms Two tenths to 0 25 c c is injected first After 3 weeks 0 4 to 0 5 c c is given

Luippold and Longfellow (1942 1943 1946) proved in a long series of experiments that there is some cross protection between typhoid and paratyphoid B organisms while *S paratyphi A* does not show cross protection with any of these Salmonellae They found too that the T A B vaccine protects against the organisms from which it is prepared against *S enteritidis* and against *S typhimurium* but not against *S choleraesuis* and *S oranienburg* It has also been proved that the Vi antigen from *S ballerup* or *E coli* 5396 protects against

the Vi factor of the typhoid bacillus Luippold (1946) prepared a stable extract of the Vi antigen from *E coli* 5396/38 which is used as an additional immunizing agent but not mixed into the T A B vaccine because of the clinical reactions caused by such mixtures

Freund and Bonanto (1946) found that killed organisms injected in a lanolin oil water mixture give rise to antibodies which persist for a very long time Chime (1942) Morgan et al (1943 1945) and Linton and Jennings (1943) greatly contributed to the development of chemically purified vaccines

According to Manson Bahr (1945) the Royal Air Force of Great Britain during the war used a T A B vaccine with sodium lauryl sulfate

Alum precipitated typhoid paratyphoid vaccines were described by Leon et al (1941) and Shevchenko (1942) These vaccines are given in a single injection

Ultraviolet irradiation was used successfully for the preparation of typhoid paratyphoid vaccines by Troitskii et al (1942) and by Oliver and Bonet Maury (1946) Remlinger described a chromo vaccine (1945), Ruiz Merino (1946) a brilliant green vaccine

Oral vaccination is not used in the Americas Perhaps the last proof of the uselessness of such vaccines was supplied by Moor and Wallace (1941)

Much interest is paid to intracutaneous T A B vaccination This method was found very effective by Leme and Carrijo (1943) and Carrijo et al (1945) The intervals and dosage vary according to the authors

Kamp (1943) gave children weekly injections of 0 1 0 15 and 0 2 c c No generalized reactions were observed

Ristori and Schwartz (1944) injected at 3 week intervals 0 05 0 1 and 0 15 c c The results were good

Reyes (1945) used 3 injections 0 1 c c each at monthly intervals No undesired reactions were observed and the results were better than those achieved by using the classical injection route

Luippold (1946) developed a mouse protection test for the evaluation of Salmonella vaccines This test together with the determination of the amount of mouse protective antibodies in the serum of the vaccinated individuals is the best measure for the control of the immunization

The many million doses of T A B vaccine given during the war proved its prophylactic value and innocuousness Tilden and Arnold (1943) however described histiocytic reactions after intradermal injections which persisted for many months de Monte and Gupta (1941) brought up the question of the so called provocative typhoid which is observed when exposed persons are immunized It is believed that if the Vi antigen is used a negative phase of a few days duration does not develop after the injection of the vaccine and consequently the vaccinated person does not become more susceptible to typhoid fever during the negative phase

It is recommended that every year revaccination be carried out with a single dose of the vaccine

SHIGELLOSIS

(Bacillary Dysentery)

DEFINITION

The terms "shigellosis" and "bacillary dysentery" are frequently used to designate the *same disease* *Shigellosis, however, is the correct name of infections caused by Shigellae* Bacillary dysentery is a clinical syndrome consisting of frequent bowel movements with the evacuation of mucus and, in many cases, blood or pus Bacillary dysentery is most frequently due to Shigellae Neter (1942) and others proved that bacteria other than Shigellae *may also cause bacillary dysentery, chiefly in children and old persons* Paracolon organisms, Protei, and Pseudomonades are often the agents of such disturbances While discussion is still progressing on the pathogenic power of certain paracolon and Proteus strains, most Shigellae found in man are considered pathogenic

ETIOLOGY

Shigellae are gram negative, nonspore forming, noncapsulated, nonmotile organisms which form acid but not gas from dextrose and, frequently, also from other carbohydrates They grow well on the usual media under aerobic and anaerobic conditions They do not produce acetylmethylcarbinol

The present American classification of Shigellae is based upon the studies of Neter (1942) According to Neter, Shigellae may be divided into four groups

I Mannitol negative, lactose negative—*Sh dysenteriae* Shiga and Sachs, *Sh ambigua* Schmitz, and *Sh newcastle*

II Mannitol positive, lactose negative—*Sh paradysenteriae* and *Sh alkalescens*

III Mannitol negative, lactose positive—no human pathogen

IV Mannitol positive, lactose positive—*Sh sonnei* and *Sh dispar*

Sh dysenteriae Shiga and Sachs are very rare in America. *Sh ambigua* is more frequent, especially in South America

The most frequent strains of *Sh paradysenteriae* are I, II, III, IV, and VI. The geography of these types was recently discussed by Hardy (1945), Hardy et al (1942, 1945), Kuhns (1943), Fulton (1945), and Nelson et al (1946) in North America, Macumber (1942) in Panama, Pot (1945) in Curacao, Hormaeche et al (1943) in South America, Fortune and Ferris (1945) in New Guinea, Nelson et al (1945) in India, Yañez (1944) in Spain, Westermann (1944) in the Netherlands, Elrod and Wormus (1946) in France, Boyd (1946) in the Middle East, and Young (1947) in global relations It seems that Boyd's 88 type is rapidly spreading It was disseminated over Europe by the German Army

Sh alkalescens is not considered pathogenic by most authors

Sh sonnei was first described by Duval in America but it is often called the Sonne Kruse bacillus The designation "*Shigella sonnei*" seems to be firmly entrenched Because of the mild clinical form produced by this organism, the disease is often diagnosed as "food upset," "summer diarrhea," "institutional diarrhea," or "just a simple intestinal indisposition " Many cases are reported from children's institutions, mental hospitals, and military camps *Sh sonnei* infections are observed in all parts of the world

Sh dispar includes *Sh ceylonensis* and *Sh madampensis* The pathogenicity of *Sh dispar* has been questioned by most authors

EPIDEMIOLOGY

The *means of spread* of Shigellae have been discussed by Neter (1943), Manson Bahr (1943), and Kuhns (1943)

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regurgitate or more commonly deposit the material by defecation Food contaminated in this way readily becomes the source of shigellosis

Water is another important source of shigellosis Shigellae may survive for a long time in untreated water Several water borne epidemics of shigellosis have been described The authors observed one such outbreak in a community of 7 000 people when the sewer broke into the water pipe line at the same time that chlorination failed

Milk may be contaminated during handling by carrier food handlers Pasteurization however readily kills Shigellae Water from a contaminated source used to wash bottles in a dairy may cause infection of the milk (Green and McLeod 1943)

PATHOLOGY

In the presentation of the pathology of shigellosis and in the discussion of its clinical symptoms the classical descriptions of Manson Bahr (1943) will be followed

Shigellosis causes acute or chronic changes in the intestines The pathology shows different degrees of severity Each of these may be accompanied by a specific clinical picture Exceptions from this rule however, are not very rare

The inflammatory changes are most often localized in the lower part of the bowel The rectosigmoid the descending colon the flexures and the cecum are frequently involved The lowest part of the ileum also may show pathology Round cell infiltrations hemorrhages necrosis with subsequent ulcerations and in chronic cases with fibrosis and hypertrophy are the basic features It is not clear as yet how much must be ascribed to the role of the excretion of absorbed toxins in the production of these changes A sympatheticotonic reaction of the intestine has been described by several authors

In acute cases the mucous membrane shows inflammation Hyperemia is present with dilated capillaries and veins This hyperemia of the follicles is characteristic in the beginning of the process Edema and hemorrhages follow chiefly in the submucosa Neutrophilic leucocytes and macrophages originating from the capillary endothelium of the bowel contribute to the infiltrates The capillaries show thrombosis Blood extravasation also occurs

As a result of these changes necrosis ensues Irregular snail track like' ulcers develop often on the summits of the mucosal folds These ulcers may be superficial or they may reach to the muscularis The size of the ulcers varies They often communicate by channels or sinuses The communicating channels may extend under the hypertrophic mucosa

Necrosis of the superficial layers may lead to the formation of diphtheroid pseudomembranes Or a necrotic mass may cover the entire intestine This mass is usually green or black due to altered hemoglobin and bile pigments When the pseudomembranes or the coagula fall off ulcerated surfaces become apparent In other cases much granulation tissue is seen

In fulminating cases the entire bowel is very *friable and much bleeding* occurs The lumen is obstructed with mucous and bloody masses

Children suffer very frequently from shigellosis The younger the child, the greater the danger of a fatal outcome of the disease Biocca (1941) found that in some states of Brazil 30 to 35 per cent of deaths in children under 2 years of age are due to shigellosis The statistics of Hormaeche et al (1943) confirm the frequency of this infection among children When we discount Shigella cultures received from the Armed Forces and isolated from veterans in our statistics children have been the source of more than 70 per cent of the Shigellae typed in this center

Army camps frequently suffer from shigellosis As Bargen (1945) points out such epidemics have occurred mostly during the period when the camp was being put into use and disappeared later when hygienic measures became firmly established

Shigellosis used to be a scourge of the armies The great epidemics of this disease during the South African War and the Gallipoli campaign discussed by Manson Bahr (1943) were not repeated in the second world war, due to the use of sulfonamides better sanitary conditions, and educational efforts

Persons suffering from other diseases such as malaria kala azar tuberculosis or malnutrition are more likely to contract shigellosis The same holds true of mental patients and old people Thousands of inmates of German and Hungarian concentration camps died from shigellosis superimposed over extreme malnutrition This condition was called the Ukraine diarrhea "

Shigellosis spreads readily among people living under crowded conditions as in some mental hospitals prisons and Indian bazaars where the rules of hygiene are not kept either because of weakened mental abilities of the inmates or because of the personal ignorance of the inhabitants

Carriers are very dangerous Only human carriers of shigellosis are known to date Convalescent carriers excrete Shigellae long after the dysentery has healed Many such carriers are intermittent carriers ' who excrete the organisms only during certain periods of time These are easily overlooked when the stool examinations are not repeated Inadequate treatment with sulfonamides or antibiotics unfortunately aids in producing a carrier state Symptomless carriers' and contact carriers have never to their knowledge shown symptoms of shigellosis Transitory carrier states are often observed in overcrowded hospitals or isolation wards where cases or carriers of different Shigella strains are congregated

About 3 per cent of persons who have suffered from shigellosis become chronic carriers *Sh sonnei* very frequently produces this condition while *Sh parad) senteriae* carriers are more often intermittent carriers The greatest danger of carriers arises when they are used as food handlers cooks waiters, dairymen packers in the food industry etc

Food is a frequent vehicle of shigellosis It may be contaminated not only by carriers but also by human excreta used as fertilizer

Manson Bahr (1943) first proved the role of the housefly in the propagation of shigellosis Houseflies may carry feces containing Shigellae on their wings legs or proboscides They may swallow infected feces and either

3 Fulminating dysentery, which includes the gangrenous and the cholera form subtypes
4 Relapsing dysentery
5 Chronic dysentery
6 Sonne dysentery

This classification will be followed in this chapter, except for the sequence of the forms

Catarrhal Dysentery

The onset is often slow In many cases, however, the beginning is sudden The first symptom is diarrhea consisting of frequent evacuation of the bowel Usually 3 to 12 stools are produced during the day These consist first of soft feces later becoming bilious and watery Their volume decreases Mucus is a characteristic ingredient of the stools

There is little or no fever The tongue is clean Prostration may be present

Cramps and straining are the chief complaints The griping is more severe when the lesions are nearer to the cecum while tenesmus predominates when the pathology is more extensive in the rectosigmoid Tenesmus, however usually develops only after several bowel movements

Vomiting is rare

This clinical form is most often due to *Sh sonnei Sh alkalescens* or *Sh ambigua*, rarely to *Sh paradysenteriae*

Shigella Food Poisoning

Shigellosis contracted by eating food contaminated with Shigellae may follow any of the several clinical forms of this disease In a number of cases however perhaps due to the toxins of Shigellae present in the food or as a sequela of the presence of some additional organism capable of causing food poisoning this clinical picture is observed

The onset is sudden in most persons who have participated in the infected meal

There is diarrhea with 4 to 15 stools a day The feces are light colored yellow or green Much mucus is present

The tongue is clean or coated There may be some fever Prostration is present

Cramps increasing into colic are always observed Griping pains are more frequent than tenesmus

Nausea and vomiting are regularly present

This clinical form is most often due to *Sh sonnei* or *Sh alkalescens* less frequently to *Sh paradysenteriae*

Sonne Dysentery

The onset is sudden or insidious In the latter case frequent bowel movements without discomfort introduce the disease The diarrhea consists of stools which are at first brown then yellow or green "Tomato soup" stools are often seen Mucus is always present in the feces

In a well developed shigellosis the intestine is edematous inelastic and contracted

Round cell infiltrations of the mesenteric lymph glands are very frequent

The spleen is congested The kidneys may show patchy glomerular congestion tubular necrosis and cloudy swelling A lymphoid peritonitis may accompany severe and fulminating inflammations

Perforations are very rare

Chronic shigellosis is a common disease but the diagnosis is frequently missed It is characterized by productive and ulcerative lesions Any of these two components may predominate The picture is frequently very colorful

The ulcers may be shallow or deep They do not have undermined edges The ulcers follow the direction of the mucosal folds They have dirty gray or brown bases The mucosa is swollen and often granular In some instances the entire mucosa is destroyed



Fig 153 —Section through colon in bacillary dysentery showing type of infiltration.

The fibrotic reaction is strongest in the mucosa and in the submucosa Scarring even stenosis may result

Pseudopolyposis is not rare

Manson Bahr s retention cysts are pseudoadenomata which cause jelly like elevations of the mucosa They may be disseminated over the entire intestine The retention cysts contain mucus and usually a large number of Shigellae Their presence causes frequent reinfections and the carrier state

Secondary infection or a double infection with Shigellae and *Endamoeba histolytica* may produce aberrant pictures

SYMPTOMATOLOGY

The incubation time is 1 to 10 days

Manson Bahr (1943) divided shigellosis into the following clinical forms

1 Mild dysentery the catarrhal form
2 Acute dysentery the classical bacillary dysentery

This type of shigellosis is caused by *Sh. dysenteriae*. Clostridia are thought to play a great role as secondary invaders.

Choleriform Dysentery

This is a fulminating shigellosis usually with a fatal outcome.

The course of the disease is characterized by subnormal temperatures, circulatory weakness and liquid offensive stools.

This type of shigellosis is caused by *Sh. dysenteriae*. We have observed it also in institutionalized old people. The etiologic agents were *Sh. dysenteriae* and *Sh. paradysenteriae*.

Relapsing Dysentery

Relapses of dysentery may occur in any clinical form. They are most often observed, however, in the classical type of shigellosis.

A new attack of dysentery develops when the patient has already begun to recuperate. Such relapses may last for variable lengths of time. Before the introduction of sulfonamides relapses were of varying severity. At present, however, the intensity and duration depend upon the medication. Relapses are often observed when too small doses are given or when the drug is discontinued too soon.

Chronic Shigellosis

Chronic shigellosis is one of the greatest problems of gastroenterology and much deserved attention is paid to it in contemporary literature. Manson-Bahr (1943), D'Antoni (1943), Silverman and Friedrichs (1943), Bargen (1945), and Felsen (1945) contributed much to the knowledge of the disease.

The clinical picture very often resembles amebic dysentery, or in some cases the sequelae—ulcerative colitis, "irritable colon," etc.—are prominent, and only bacteriologic, sigmoidoscopic and x-ray examination will reveal the real cause of the sickness.

The disease may begin as a chronic shigellosis per se, with an attack of diarrhea and in some cases fever. The stools may contain a varying amount of blood and mucus. This state may last, with shorter or longer remissions or intermissions, for a very long period of time.

In other cases the patient recuperates after an attack of acute shigellosis only to develop, after months or even years, a state of alternating diarrhea and constipation. The initial attack may have been so mild that it was overlooked.

In some instances diarrhea is scarcely present; rather, the patient has constipation. In these cases psychoneurotic symptoms may be prominent. There is fatigue, lassitude, inability to concentrate, morning headaches and alterations of the appetite. Abdominal discomfort with feeling of pressure or even pain along the descending colon and rectosigmoid, in the flexures or over the appendiceal region, may be present.

There may or may not be fever The tongue is clean or white Prostration is usually present

Cramps and colic griping pains and tenesmus may be present Griping pains are very frequent chiefly at the beginning of the illness

Nausea and vomiting are often observed

A respiratory catarrh is the characteristic feature of this clinical form of shigellosis The disease often begins with pharyngitis or bronchitis and the diarrhea appears only a few days later Catarrhs of the respiratory tract may dominate the clinical picture so that the diagnosis of an influenza attack later eventually modified with an *epitheton ornans* and called ' intestinal flu ' may be born

Epidemics of Sonne dysentery resembling 'intestinal flu' frequently occur in large cities An accumulation of such cases was observed in 1946 among children in Chicago

It must be emphasized that *Sh sonnei* infections often cause other clinical types of shigellosis

Classical Bacillary Dysentery

The classical type of shigellosis is classified by Manson Bahr as "acute dysentery "

The onset is usually sudden The disease however may begin as a single diarrhea without characteristic stools The diarrhea when fully developed is severe As many as 20 to 40 stools are evacuated each day They are first feculent then mucus and blood appear in them The mucus may be bile stained The amount of the feces decreases so that only small masses of viscid jelly like bloody mucus are evacuated These stools resemble ' red currant jelly or meat washings " The stools are odorless or have an albuminous odor If gangrene complicates the disease the stools become gray and are very offensive

Fever is usually present It does not usually exceed 103° F The face is flushed The tongue is white or coated Great prostration is present

The cramps and colic are severe There is straining griping pains and tenesmus are present according to the localization of the process

Vomiting is rather rare

Dysuria is frequent

Upon physical examination the abdominal muscles are rigid and make palpation difficult When they relax the contracted spastic colon may be felt

This clinical form of shigellosis is usually due to Sh dysenteriae Sh ambigua and Sh paradysenteriae

Gangrenous Dysentery

This is a fulminating shigellosis usually with a fatal outcome

It begins with chills The temperature is elevated and may reach 102° to 104° F Then diarrhea develops There are usually many green or gray offensive stools The abdomen is sunken and tender The tongue is thickly coated Pain cramps and tenesmus may or may not be present The disease lasts usually only a few days

swelling of the joints The knees and the ankles are the usual seats of this complication Organisms are not recovered from the exudates but these fluids readily agglutinate Shigellae

Eye Complications—Conjunctivitis frequently accompanies Shigella arthritis Conjunctivitis alone or with iridocyclitis is rather rarely observed It occurs only *in Sh dysenteriae infections*

Reiter s Syndrome—Reiter s syndrome consisting of an aseptic urethritis conjunctivitis and arthritis is considered by some authors a sequela of shigellosis

Other Complications—Peripheral neuritis and parotitis are often mentioned as possible complications and sequelae of shigellosis They are very rare

SIGMOIDOSCOPIC FINDINGS

The sigmoidoscopic appearance of shigellosis was described in great detail by Manson Bahr (1943) and Felsen (1945)

At first small elevations with or *without a yellowish apex are observed* Then small ulcerations ensue which spread and coalesce The ulcers are irregular in size shape and extent They are not very deep

The mucosa is inflamed and reddened The entire mucosa may show inflammation Later edema appears often followed by bleeding and pus formation

In the pseudomembranous type the membranes may be seen A bleeding uneven granular surface lies under the membrane This surface is often covered with pus Frequently only remnants of the membrane resembling strings or threads are seen

Regeneration is characterized by the formation of granulation tissue The mucosa remains reddish pink for a long time *After healing* a pitted mucosa is frequently seen

The sigmoidoscopic patterns of chronic shigellosis were classified by Manson Bahr as

1 Superficial ulcerations
2 Granular mucosa
3 Generalized mucoidal inflammation with deep involution of the bowel wall

There is great irritability of the rectosigmoid during shigellosis It is recommended therefore that sigmoidoscopic examinations be carried out only by proctologists or physicians with considerable experience in the handling of this instrument

X RAY EXAMINATION

The x ray picture of shigellosis has been mentioned *in Chapter 4* Due to the acute course of most cases of shigellosis not much material is available for such studies Bargen (1945) called attention to the irregular and yet extensive distribution of Shigella ulcers which may be observed by studies of the mucosal pattern of the bowel

Complications and Sequelae

It is sometimes difficult to draw a dividing line between complications and sequelae They are therefore discussed under the same heading

Ulcerative Colitis—Ulcerative colitis with a chronic course is a frequent sequela of shigellosis The transition is usually slow and gradual In many cases however the beginning of the ulcerative colitis is severe The sigmoidoscopic picture and the course of the disease do not differ from those observed in the so called nonspecific ulcerative colitis originated by other factors Felsen (1945) made excellent contributions to this subject

Regional Ileocolitis—Regional ileitis and colitis may be caused by bacillary dysentery This sequela is relatively rare

Deformities and Hypertrophy of the Colon—Narrowing of the lumen is a frequent sequela of deep ulcerations Stenosis may also develop Megacolon is infrequent Into this group belong prolapse of the rectum and polyposis While prolapse is more often observed in children polyposis is more frequent in adults

Nutritional Disturbances—Many patients suffering from chronic shigellosis become sensitized against certain foods chiefly against milk and eggs Such allergies must be kept in mind when the patient s diet is compiled

Nutritional deficiencies are more frequent in shigellosis than is commonly thought There is an impaired absorption of members of the vitamin B group The metabolism of vitamin K is also frequently disturbed

Nutritional deficiencies may become very severe The walking skeletons of the tropics are frequently the results of Shigella infections

Functional Disturbances of the Digestive Tract—The formation of several digestive enzymes may be impaired Dyschlorhydria usually in the form of hypochlorhydria is common

Mucous colitis is very frequent A so called irritable colon is observed in most cases of chronic shigellosis and may appear in any patient as a sequela of an acute shigellosis

Ascites is not rarely seen in India following shigellosis This sequela is very rare in the Americas

Perforation—Perforation of the bowel rarely occurs in shigellosis The symptoms are those observed in perforations due to other diseases

Urogenital Apparatus—Shigella pyelitis has been observed Pregnant women seem to be more frequently attacked by this form of shigellosis than other members of the general population (Haynes et al 1941 and Biddle and McKee 1942)

Pyelitis cystitis and urethritis caused by other bacteria are not infrequent complications of shigellosis

The kidneys are under great stress during the disease In many fatal cases death occurs as a result of renal insufficiency

Arthritis—Arthritis is observed only in *Sh dysenteriae* infections It usually develops during the period of convalescence There is fever and

30 000 cells The number of white blood cells decreases during the further course of the disease

Anemia develops in severe shigellosis *Due to the dehydration the number* of red blood cells may remain normal even in such cases

DIFFERENTIAL DIAGNOSIS

The only decisive factor for the diagnosis of shigellosis is the cultural proof of the presence of Shigellae in the feces When however the patient has been given sulfonamide therapy before a sample is taken for laboratory examination the bacteriologic diagnosis is greatly endangered Except under the most primitive conditions one cannot find any excuse for omitting such an examination Modern preserving fluids and present day transportation facilities permit the delivery of a fecal sample to a laboratory *in most* cases

The bacteriologic examination may be more difficult in chronic bacillary dysentery As Manson Bahr (1943) pointed out it is extremely difficult to recover Shigellae from a chronic dysenteric granulosis of the rectosigmoid When ulcerative colitis has developed the organisms are rarely found

Bacteriologic and parasitologic examination will differentiate amebiasis *giardiasis salmonellosis schistosomiasis tuberculosis and other infections* Inguinal adenitis and a positive Frei test are characteristic for lymphogranuloma venereum Blood examination will exclude malarial dysentery Positive serologic tests characterize syphilis of the bowel Intestinal actinomycosis is rare and usually shows different lesions when examined sigmoidoscopically

A diagnosis of sprue must be made from the appearance of the stools flat glucose tolerance curve a steatorrhea and typical x ray picture

*A carcinoma of the rectosigmoid may cause considerable diagnostic diffi*culties The sigmoidoscope and the x ray are the most potent aids in establishing the presence of this neoplasm

Diverticulitis intussusception foreign bodies hemorrhoids thyrotoxicosis uremia poisoning with mercury and arsenic also must be considered when the diagnosis of shigellosis is made

PROGNOSIS

The over all mortality of shigellosis is 4 to 5 per cent It is higher in children and in older people The prognosis is grave in fulminating forms *Sh dysenteriae* infections formerly caused mortality rates as high as 25 to 50 per cent before the advent of the sulfonamides At present the fatality rate is considerably lower

Manson Bahr (1943 1945) calls attention to the necessity of watching the stools the tongue and the pulse during shigellosis because *the prognosis* is based upon observation of these conditions

LABORATORY EXAMINATION

Stool Examination

Shigellae are only exceptionally isolated from the blood and from the urine The examination of the stools is therefore the only available means for detection of these organisms

Many Shigella strains are fastidious Nonselective and medium-selective plates must be used for this reason The SS agar (Difco) and DEC plate of Panja and Ghosh the DCLS medium (Baltimore Biological Laboratory) MacConkey s plate and eosin methylene blue agar are most often inoculated Several plates should be streaked with each specimen or when the results are negative the examination should be repeated

An excellent method to collect material is the rectal swab technic devised by Hardy et al (1942) See Chapters 71 and 72

The colonies isolated on the diagnostic plates are identified according to the procedure described in Gradwohl *Clinical Laboratory Methods and Diagnosis* vol 2 1948

Agglutination Tests

Agglutination tests using the patient s serum and antigens prepared from Shigellae are of little value Hulst (1940) Draper (1945) and others proved that so called natural agglutinins may be present in healthy individuals On the other hand agglutinating bodies develop late in the disease usually during the second or third week when the diagnosis has already been easily established by stool examination Their titers are frequently low Agglutination with serum dilutions 1 100 and higher are usually considered positive Many cross reactions are observed with paracolon organisms and other bacteria The value of the agglutination test is therefore very problematic

Cytology of the Stools

Much attention should be paid to the cellular composition of the stools Red blood cells and polymorphonuclear leucocytes are often present Macrophages with remnants of engulfed cells and cell fragments are frequent They are readily mistaken for amebae except in hematoxylin stained preparations There is much debris present It must be pointed out that in catarrhal shigellosis the number of cells may be very small Mucus is however always present

Young leucocytes and macrophages are numerous when ulcerations are forming Their number diminishes during healing At the end of the disease old leucocytes with pyknotic nuclei and numerous epithelial cells dominate the picture The cellular elements are often embedded in streaks of mucus

Hematology

The peripheral blood does not show great changes In the beginning chiefly in severe cases however there may be a leucocytosis with as many as

Insufficient urinary output is a contraindication for sulfonamide medication

It is good practice to begin the treatment of acute toxic shigellosis with 5 to 6 Gm of sulfadiazine divided into 5 or 6 doses during the first day then 3 Gm of sulfaguanidine *or* 4 Gm of sulfasuxidine *or* 2 Gm of Sulfaphthalidine every 4 hours until the number of stools is 4 or less per day finally the same amount of the selected sulfonamide 3 times a day until the stools become normal for 2 days

In cases which do not show toxic symptoms 3 5 Gm of sulfaguanidine or 5 Gm of sulfasuxidine *or* 2 Gm of Sulfaphthalidine are given 4 times a day until the stools become normal for 2 days

In chronic cases 0 5 Gm of sulfadiazine *and* 2 Gm sulfasuxidine 4 times a day for 14 days the course repeated after 14 days intermission has proved beneficial Good results have also been seen by giving 1 Gm Sulfaphthalidine 4 times a day for the same periods of time

Recently phthalyl sulfacetimide (Thalamyd) has been introduced in the treatment of shigellosis This drug is only very slightly absorbed but it penetrates the intestinal mucosa It has proved very effective in the therapy of bacillary dysentery ulcerative colitis and cholera Adults receive 6 to 9 Gm daily children 0 2 Gm per kilogram body weight per day

Vaccine Therapy

Vaccine therapy is recommended in chronic shigellosis Autogenous vaccines are used Berge and Fauconnier (1941) recommend this treatment

Bacteriophage

Soesman (1941) McKay (1943) and Burke (1944) recommend this therapy Boyd and Portnoy (1944) and Morton and Engley (1945) reject it It is little used in the Americas The bacteriophage is given orally or per rectum 2 c c daily

Dietary Treatment

During the acute stage of dysentery an easily digested high caloric diet rich in *vitamins and low in residue is given*

The fluid intake must be 4 to 6 liters a day Weak tea rice water and soups are recommended Fruit juices are not always well tolerated Orange Crush may be tried Lactose or sucrose is added to the fluids to increase their caloric value

It is advisable to give only fluids during the first and second days of the disease The diet is supplemented later with jellies and egg yolk Amino acids *usually 2 teaspoonfuls 3 times a day are beneficial*

When gross bleeding has stopped puddings custards chocolate and malted milk butter, toast crackers well cooked rice and tapioca are added

In chronic dysentery the diet described under 'Amebiasis will render excellent service

TREATMENT*

Fluid Intake

The most important part of the therapy is to assure an adequate intake o fluids. The daily urinary output *must* be kept above 1,500 c.c.

If a proper urinary output cannot be achieved by oral administration in fusions with 5 per cent glucose are recommended. As much as 4 liters can b given daily. The average dose is 2 to 3 liters per day.

Serum Therapy

Forty to 50 c.c. of specific or polyvalent serum are given intravenousl twice a day in 250 to 500 c.c. of physiologic saline. The serotherapy must b begun early. There is no need to give serum during the later days of th disease.

The serotherapy must be limited to toxic cases. Because of the larg amounts of serum necessary to combat the symptoms, desensitization is nece sary prior to the injections.

One hundred fifty to 200 c.c. of convalescent serum or plasma give goo results.

Whole blood (250 to 500 c.c. daily) is very beneficial in toxic cases.

General Measures

It is very important that every patient with an acute shigellosis or wit an attack of a recurrent chronic dysentery remain in bed.

The patient must be kept warm.

Sulfonamide Drugs

The critical evaluations of sulfonamides in dysentery by Lyon (1941 Hardy et al. (1943), Bose et al. (1945) and Bargen (1946) show that a dru must be chosen according to the case and that the patient and *not* the disea must be treated. Hardy et al. (1943) and Woodrow and Douglas-Henr (1945) recommended sulfadiazine. Bulmer and Priest (1942), West (1943 Fairley and Boyd (1943), Page (1944) and Yannet et al. (1944) were satisfie with sulfaguanidine. Kuhns (1943), Manson-Bahr (1945) and Bargen (194 recommended a choice between sulfaguanidine and sulfasuxidine, the latt being less toxic but perhaps also less active. Streicher (1945) had exceller results with Sulfaphthalidine which is now being used on a larger scale.

Sulfonamide drugs must not be given for a longer period than 14 day During the treatment frequent urine examinations must be carried out and th drug discontinued whenever an excess is present in the urine. Period hematologic examinations are also indispensable to avoid damage to th hematopoietic system.

Two to 4 Gm. of sodium bicarbonate must be given with each dose o sulfonamide drugs.

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*Recently antibiotics, aureomycin, Chloromycetin, terramycin and neomycin per os ha been recommended.

stools with the aid of the Hardy swab or through the proctoscope and also to examine postcathartic fecal specimens because of the varying sites of the lesions

A carrier must be checked at least for 3 months before release During this period at least 6 stools must be examined

Carriers of *Sh sonnei* are frequently refractory to sulfonamide medication Changing from one drug to the other is recommended in such cases

There is little use in examining the stools for Shigellae during sulfonamide treatment because the medication may inhibit the growth of Shigellae on diagnostic plates The first release specimen must not be taken earlier than 1 week after the sulfonamide administration has been discontinued

Carriers often require prolonged sulfonamide treatment It must be kept in mind that this medication also reduces the number of organisms which are necessary for certain normal physiologic functions of the bowel Care must be exerted therefore to avoid both sulfonamide intoxication and nutritional disturbances

PROPHYLAXIS

General rules for the extermination of shigellosis may be summarized as

1 Control of Carriers

No food handler harboring and excreting Shigellae shall be allowed to handle or prepare food Repeated stool examinations before and during employment are necessary to detect carrier food handlers It is important that not only food handlers in the usual sense (waiters cooks cowhands dairy workers food packers etc) *be examined but also nurses and maids who nurse* and feed children

2 Food Control

Shigellae pathogenic for man do not occur in animals the meat milk or eggs of which are used for human consumption Protection of food from infection by human carriers flies and contaminated water will therefore keep food free from Shigellae

3 Water and Sewage

Water borne shigellosis is more frequent than is generally thought The water may *be contaminated with sewage either by seepage or by direct* evacuation of such material into it

Chlorination or boiling destroys Shigellae promptly

4 Flies

Flies are dangerous vectors of shigellosis One of the most efficient measures in the campaign against shigellosis is screening or other methods which keep flies away from food

5 Vaccination

Much progress has been made in vaccination against shigellosis during *the last years As Weil and Farsetta (1944 1945)* proved the specific anti

Intestinal Absorbents and Aperients

Kaolin and its combinations as Kaopectate Kaomagma etc are helpful for the absorption of the toxins These are indicated during the diarrhea or when much flatulence is present If absorbents are given, the sulfonamide medication must be timed in such a way that these drugs are not absorbed (and thus inactivated) by the kaolin

Many authors advocate the use of aperients before treatment As Manson Bahr (1943 1945) points out saline cathartics must not be given in dehydrated cases because they cause further loss of water One tablespoon (4 Gm) of sodium sulfate in about 150 to 200 c c warm water is the best cathartic in constipation during chronic dysentery

Relief of Pain

Heat is essential in the treatment of dysentery Dry hot pads or pillows placed on the abdomen relieve pain and cramps Short hot baths are also useful

Lavages with 0 1 to 0 2 per cent potassium permanganate may be used in cases with pseudomembranes Washings of the bowels with 1 5 per cent tepid boric acid serve the same purpose

Opium morphine and papaverine render excellent services in the treatment of acute shigellosis They may be given in injections in enemas or in suppositories It is recommended that these drugs be combined with belladonna A small dose of barbiturates may be added

℞ Tinct opii 30 min
Tinct belladonnae 10 min
Elix phenobarbitur 20 min
Starch and water q s ad 2 oz
S Enema

℞ Papaverin sulf 0 3 Gm
Atropin sulf 0 002 Gm
Ol Cacao q s u ft suppos no 10
S One suppository 1 3 times a day

Treatment of Complications

Ulcerative colitis is treated with sulfonamides dietary and other measures used in that disease if caused by other factors

The prognosis of ulcerative colitis *quoad sanationem* is not favorable If surgical treatment is advised Manson Bahr (1943 1945) favors appendicostomy

Nutritional disturbances are treated with proper diet and injections of vitamins

Sulfonamide drugs and heat are recommended in arthritis and in eye complications

Treatment of Carriers

The sulfonamide treatment of carriers must be planned as in chronic shigellosis In order to be able to check the results of this therapy several stool specimens must be examined It is of paramount importance to collect

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gens which are different for each type of Shigella play a great role in immunity Because of the great number of types it is very difficult to produce polyvalent vaccines In addition Shigella vaccines cause severe reactions

Morgan and Partridge (1941) used alkali treated material for immunization Halbert et al (1945) reduced the toxicity of the antigens by injecting saline in mineral oil emulsions Treffers (1946) found that acetylated antigens are less toxic Olitzki and Koch (1945) worked out a special method for the production of effective antigens

While whole organisms or their extracts are used for vaccination against *Sh paradysenteriae* *Sh ambigua* and *Sh sonnei* formolized toxin (toxoid or anatoxin) is injected very often for the protection against shigellosis caused by *Sh dysenteriae* the only member of the genus which produces a true toxin

Olitzki and Koch (1945) Farrell (1943) Anderson et al (1945) and Dubos and Geiger (1946) recently made considerable contributions to the technic of the preparation of *Sh dysenteriae* toxoid Farrell et al (1944) has had good experiences with it in human volunteers Olitzki and Koch (1945) have observed excellent results in a great number of exposed persons

Experiments on volunteers with vaccines were performed by Morgan and Schutze (1943) and Goebel et al (1945) Cooper et al (1944) immunized children with a *Sh paradysenteriae* vaccine and found that intravenous injections cause the greatest elevation of mouse protective antibodies Forsyth (1942) and Felsenfeld and Young (1945) prepared mixed vaccines against *Sh dysenteriae* and *Sh paradysenteriae*

Proper hygienic measures and the encouraging results of sulfonamide treatment have greatly reduced the necessity for antishigellosis vaccination Such vaccination is still advisable however Toxoid injections and during epidemics vaccines prepared from the strains which cause the outbreaks are indicated in the tropics

Prophylaxis with the aid of dysentery bacteriophage is recommended by Dumesh (1942 but is rarely used in the Americas

6 Drug Prophylaxis

Sulfadiazine or Sulfaphthalidine 0 5 Gm twice a day are said to be effective for the prophylaxis of shigellosis

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CHAPTER 30

SALMONELLOSIS, TYPHOID FEVER, SHIGELLOSIS IN CHILDREN

SALMONELLOSIS IN CHILDREN

ANTONIO SELLEK

TYPHOID FEVER IN CHILDREN

ANTONIO SELLEK
GUSTAVO CARDELLE
JUAN A. JIMENEZ

SHIGELLOSIS IN CHILDREN

ANTONIO SELLEK

SALMONELLOSIS IN CHILDREN

Hormaeche and Peluffo define salmonellosis as "an infectious contagious disease which presents all the characteristics and manifestations of a true infection, with progressive development, variety of localizations and high mortality."

The immunology, epidemiology and bacteriology have been discussed in Gradwohl (1948).

Biochemical characteristics routinely used in identifying Salmonellae do not easily differentiate them from paracolons, which are "slow" fermenters of lactose and sucrose. Paracolons also seem to occupy an important position in pathology; they have frequently been isolated from cases of acute enteritis. Curbelo Hernandez, Soto Pradera and Montalvo Urrutibeascoa reported (1945) an outbreak of gastroenteritis due to paracolons among newborn infants.

BACTERIOLOGIC EXAMINATION OF SALMONELLOSIS BY CULTURE

The following method is used by us for fecal material.*

When the samples are to be sent from a distance, the Teague and Clurman mixture is used. (This is a sterile 30 per cent buffered glycerin in saline solution.) A fresh feces specimen or, better, mucus, pus, or blood when available, is inoculated in an enrichment medium (selenite F or tetrathionate broth) *as well as seeded directly, after* previous washing, on such media as SS agar and MacConkey agar. All are incubated for 18 to 24 hours. From the enrichment medium, seedings are made in SS agar and MacConkey agar.

Tetrathionate broth, SS agar, and MacConkey agar are considered excellent. Suspected *colonies are transferred to tubes of plain broth containing* the sugar series. If the

Photographs in this chapter are from autopsies made during an epidemic outbreak of meningitis in the newborn by *Salmonella havana*. Studies made by Angel A. Aballi and collaborators in the Municipal Children's Hospital in Havana. (*21 cases*)

*For a different procedure see Chapter 71.

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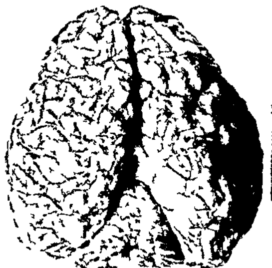


Fig 160—Purulent meningitis (salmonellosis) covering the cerebellum. (Courtesy of F Sala Panisello Children's Municipal Hospital of Havana

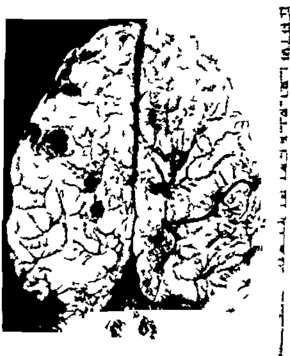


Fig 161—Purulent *meningitis with hemorrhagic foci* disseminated through the left hemisphere branching into the other hemisphere (Meningitis due to *Salmonella havana*) (Courtesy of F Sala Panisello Children's Municipal Hospital of Havana)

organism is gram negative, motile, produces acid and gas in glucose,* mannitol, maltose, and sorbitol, does not produce indol nor ferment lactose, it is suspected of belonging to the genus Salmonella. Serologic identification is too complicated for routine hospital laboratory use. The agglutination tests for antigenic analysis can be made in Salmonella Centers† or in well equipped laboratories with experienced personnel.

Where proper equipment is lacking and there is no Center available for the necessary service, pediatricians must be guided solely by the characteristics of the genus.‡

Blood Culture.—Blood culture is very important as an early step in the isolation of strains of Salmonella with great invasive power. Blood cultures are often positive, while the feces are negative.

Salmonellae in Cerebrospinal Fluid.—Salmonellae are present in the cerebrospinal fluid in cases of Salmonella meningitis. Twenty-one cases of meningitis in the newborn were studied in this hospital by Curbelo and Martinez Cruz. In 1940 Guerra Peluffo and Aleppo reviewed the literature and collected 56 cases of meningitis due to Salmonella. Seter later compiled 22 cases. The species most frequently found were *S. schottmuelleri* 8 cases, *S. typhimurium* 17, *S. choleraesuis* 5, *S. enteritidis* 34, and 13 cases were of a heterogeneous group of species (*havana, dublin, eastbourne, jena,§ london*). In Cuba, Valledor et al. reported a case of meningitis due to *S. eastbourne* which was cured by sulfapyridine and sulfadiazine.

Salmonellae may also be isolated from cultures of urine, pleural fluid, peritoneal fluid, etc.

FREQUENCY

Incidence of the different types of Salmonellae may vary in different countries and even in different localities in the same country. See Chapter 29.

CLINICAL SYMPTOMS

The majority of our cases in children during the early days of their lives have been caused by a septicemic type with extraordinary intensity of infectiveness and have almost constantly been accompanied by meningoencephalitic symptoms and high fatality. During the first years of life, it is possible to observe diarrheal forms of mucogranulous or purulent mucohemorrhagic type constituting the most marked symptomatology and therefore confused with dysenteric affections in such infants.

Other cases are manifested as pyretic gastroenteritis with a typhoid pattern, and only bacteriologic investigations can establish their true nature. It is interesting to note that the choleriform syndrome may appear frequently in these cases, either as a dyspeptic type, "toxic dyspepsia," with intense dehydration, or as an episode within one of the forms indicated above, generally leading to a fatal disturbance of the acid base balance. On other occasions we have been able to verify the marked neurotropic tendency such as occurred in our epidemic of 1936. We have observed localization also in the respiratory apparatus in more or less severe form, sometimes causing fatal bronchopneumonia.

At times the septic picture is accompanied by visceral rupture which affects widely separated sites, or forms may be accompanied by arthritis and

*Exceptions are listed on page [illegible].

†Credit should be given to P. R. Edwards, the pioneer in Salmonella Centers, who contributed so much to the knowledge of salmonellosis. (O. F.)

‡Divergent opinion is to be found in Chapters [illegible] and [illegible] of this book and in Craigwohl (1948).

§[illegible] (O. F.). Not considered a species per se today.

In severe cases vitamins B_1 and C are administered during the early stages and later factors of the B complex and liver extract are injected intramuscularly In older children the first food should be fruit juices Four or five days later they may be given boiled chicken or fish and skimmed milk Regular diet was occasionally begun ten days after commencement of the diarrhea

In undernourished children blood transfusions and infusions are administered if necessary to correct dehydration

Symptomatic treatment is indicated at times tincture of paregoric is used against tenesmus and diarrhea Stimulants such as adrenalin and Coramine are given in syncope

Treatment with sulfonamide drugs combined with dietary and symptomatic medication is the classical treatment Agustin Castellaños published studies of major interest on this subject Insoluble forms of the drug (sulfaguanidine sulfasuxidine) are of little value in salmonellosis although these drugs are useful in shigellosis Salmonellae enter the body by way of the mouth and cause inflammatory lesions in the digestive tract The bacteria have a tendency to spread throughout the body by way of the blood stream and to localize extraintestinally Therefore according to Castellaños soluble sulfonamide drugs are to be used in treating the disease These drugs are easily absorbed and high concentrations can be reached in the blood, they act upon the bacteria not only in the intestines but also in the blood and remote organs Experimental and clinical studies dealing with the question indicate that *S choleraesuis* is greatly affected by soluble sulfonamide drugs It is possible that some serious cases caused by *S enteritidis* and *S typhimurium* may also react to these drugs According to clinical observations paratyphoid A does not seem to be affected by the soluble sulfonamide drugs although experimental studies indicate that it is susceptible to them Administration of the soluble drugs does not influence the clinical course in paratyphoid B and C infections in man In the opinion of Zerbino et al the use of sulfonamide drugs in Salmonella enteritis is efficacious when a diffusing agent is indicated Sulfathiazole (Zerbino et al) has reduced mortality from 40 per cent to 7 1 per cent

Castellaños places sulfadiazine first among the sulfonamide drugs because it is less toxic and is better tolerated sulfathiazole is placed next and then other drugs which are absorbed

The patient shows clinical improvement within 24 to 72 hours if the sulfonamide drug is effective If no improvement is noted at the end of this period another sulfonamide drug is substituted This rotation sometimes gives excellent results When lack of tolerance is indicated (vomiting) the drug may be administered parenterally intramuscularly, or intravenously as the case may require (Castellaños) In chronic cases an autogenous vaccine is indicated (Castellaños) Drugs with localized action give uncertain results

In infections due to a combination of bacteria—Shigellae associated with one or more types of Salmonella or several types of Salmonellae together—a soluble sulfonamide drug by itself will suffice *

*It is interesting to note that antibiotics are less active in Salmonellosis in children than in adults

osteomyelitis secondary anemia and even a hemorrhagic syndrome such as we had occasion to observe at an autopsy in 1936

Aballi divides salmonellosis in children into the following clinical types (1) slight digestive upset with dyspeptic syndrome (2) enterocolitis very frequently with dysenteric syndrome (3) toxic form of the infantile cholera type (4) septic form with typhoid pattern (5) neurotropic septicemia in the newborn and (6) septic form with tendency to varied localizations

The hemogram in salmonellosis may show transient leucopenia with relative lymphocytosis Later this leucopenia is superseded by leucocytosis the intensity of which depends upon the clinical course of the disease and the complications

THE WIDAL SEROREACTION IN SALMONELLA INFECTIONS

Positive agglutination reactions may be observed in patients with Salmonella infection Cross reactions however do occur Differentiation may be attempted by repeating the test every two or three days, since the agglutinins continue to increase in titer against the specific bacterium which is causing the infection In extraintestinal Salmonella infections the bacteria at times cannot be isolated from the feces, but the serum of the patient nevertheless agglutinates the organisms at very high titers

Occasionally the serum of patients infected by Salmonellae shows lack of agglutinin O titer or a very low titer for O but the agglutinins for ' H may be high these may be formed exclusively against one of the phases *

TREATMENT

Zerbino writes that 50 per cent of cases of enteric infection in Uruguay are of specific enteritis (Shigella or Salmonella) His experience was with 384 children up to 2 years of age three fourths of whom were less than one year old Aballi Jr and J A Martinez Cruz indicated that in Cuba specific enteric infections are the most frequent cause of diarrhea in well nourished children Their figures were taken from private patients (116 cases) In his work Acute Diarrhea in Infancy and Childhood Aballi (1944) suggested the following plan of treatment Except in very mild cases a period of starvation should be allowed This helps control the symptoms rapidly In cases with severe vomiting nothing is given by mouth otherwise water or tea is given For babies the quantity of liquid is 3 ounces per pound of weight every 4 hours A mixture of sodium chloride and sodium bicarbonate helps prevent the upset of the acid base balance After improvement of the diarrhea a mixture of agar and pectin is used for 12 to 36 hours This is followed by acidophilus milk After 24 to 48 hours if it is well tolerated the amount of food is increased to cover the caloric requirements

Patients on a protein free diet over a long period must be given transfusions of whole blood and plasma to prevent hypoproteinemia

* See also Chapter 78

large, pale colored mass, composed of histiocytes, some uninuclear cells, other cells with nuclei in mitosis, the majority in a state of active phagocytosis Typhoid bacilli, if present, may be seen in the cytoplasm of the macrophages They do not exhibit the delicate appearance of the bacilli from cultures, but appear as long, rod like organisms, swollen and deformed

In the usual lesions of typhoid, it is very difficult to find bacilli unless death has occurred only a few hours ago thus facilitating the growth of *S typhosa*



Fig 16? —*Left* follicular colitis *right* follicular ulcerative colitis.

Not all macrophages survive the lethal action of the toxins of the engulfed bacilli Necrosis of the cells and of adjacent tissue results, this is a typical lesion in the disease Lymphatic and blood capillaries are seen blocked by large masses of macrophages and precipitated fibrin, this thrombosis interferes with the nutrition of the tissues, thus promoting the lethal effects of the bacterial action Capillary obstruction by itself, however, is not considered responsible for the necrosis

The final result of this process is the transformation of normal lymphatic follicles of the intestinal mucosa into enlarged corpuscles of a soft, succulent consistency, this condition is found in masses of necrotic tissue which *is gray* or yellowish gray, sometimes hemorrhagic

The necrotizing process is extensive and involves the surrounding tissue, with intense ulceration of the mucosa, followed by secondary infection with in

PROGNOSIS

Prognosis is related to the age of the child The type of Salmonella is also important those belonging to group C of the Kauffmann White schema being extraordinarily malignant (Saphra)

PROPHYLAXIS

See Chapter 29

TYPHOID FEVER IN CHILDREN

Typhoid fever is an acute infectious disease caused by *Salmonella typhosa (Eberthella typhosa)*, which was discovered in 1880

That it may be transmitted from mother to fetus was first demonstrated by Eberth in 1889 (fetal or congenital typhoid) Typhoid fever in children presents certain individual features which distinguish it from typhoid fever in adults Rare in nurslings it becomes increasingly frequent as age advances This is due not to lesser susceptibility on the part of babies but rather to less opportunity for contagion It is found only exceptionally in breast fed infants although we had the opportunity of observing one case in an 8 month old child in a strongly infected area

Typhoid fever is found in all countries While absent in some regions in others it is endemic in character In tropical countries it predominates during the rainy season In general it increases in summer and decreases in winter In the temperate zones it is more frequent in autumn and early winter

PATHOLOGIC ANATOMY

Lesions of the tissues due to the typhoid bacillus involve principally the cells of the reticuloendothelial system—macrophage cells—plasma cells and lymphocytes Consequently the lymphoid tissue of the whole organism especially in the path of the primary invasion shows the most typical changes

Lesions outside the reticuloendothelial system develop secondarily often as a result of the combined action of the bacteria and physicochemical agents It is to be recalled that S typhosa is a gram negative bacillus with a complex flagellar cover It is capable of producing a strong endotoxin which is responsible for the general intoxication characteristic of the disease

Typical specific lesions in typhoid are definitely the result of the action of multiple factors

When the typhoid bacillus appears in the intestinal mucosa it is attacked by macrophages as a result of proliferation of the mucosal reticulum and that of the lymphatic follicles These cells envelop the bacilli even though the cytoplasm of such cells contains other dead cells living organisms fragments of leucocytes and lymphocytes plasma cells or red cells The engorged macrophages wander in and out of lymphatic and capillary channels and invade the neighboring lymphoid tissue

Constant proliferation of enlarged mononuclear cells occurs there is invasion of the lymphatic follicles this structure is eventually converted into a

large, pale colored mass, composed of histiocytes, some uninuclear cells, other cells with nuclei in mitosis, the majority in a state of active phagocytosis Typhoid bacilli, if present, may be seen in the cytoplasm of the macrophages They do not exhibit the delicate appearance of the bacilli from cultures, but appear as long, rod like organisms swollen and deformed

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The necrotizing process is extensive and involves the surrounding tissue, with intense ulceration of the mucosa followed by secondary infection with in

testinal bacteria Deep seated lesions, such as those of mesenteric glands, spleen liver, and bone marrow, undergo liquefaction If the patient survives the infection, these deep seated lesions heal by cicatrization or partial reparation of the destroyed tissue

If extensive necrosis or secondary infection is present, the cellular reaction is complicated by the appearance of polymorphonuclears although mononuclears continue to predominate These determine the morphologic character of the reaction Notwithstanding the fact that typical lesions may develop on a large scale in areas where there are large numbers of reticuloendothelial cells a typhoid lesion or granuloma may develop in any tissue of the system because of the specific nature of the lesions



Fig 163—Left ulcerohemorrhagic colitis right, pseudodiphtheritic colitis.

The macroscopic and microscopic characters of the granuloma differ in various organs, due to the difference in structure of the organs Lesions of the separate tissues are

Digestive Tract —Localization of lesions in the digestive tract is determined entirely by the distribution of lymphoid tissue In severe cases acute ulcerative lesions may develop in the mouth and in the pharynx When these lesions are secondarily infected large diffuse pseudodiphtheritic areas of the mucosa are formed The secondary infection conduces to the formation of large retropharyngeal and peritracheal abscesses, accompanied by necrosis of

the laryngeal tissue and by chondritis of the laryngeal and tracheal cartilages The epiglottis is not affected since it is not composed of lymphoid tissue Lesions in the mouth and in the pharynx reside in the lymphoid tissue as described above appearing first as local enlargements which ulcerate and rapidly become subject to secondary infection

The esophagus usually does not show any alterations The stomach on rare occasions presents mild, round ulcerations with a necrotic center These are situated in the lymphoid tisue They are elevated swollen greenish yellow in color with notched border

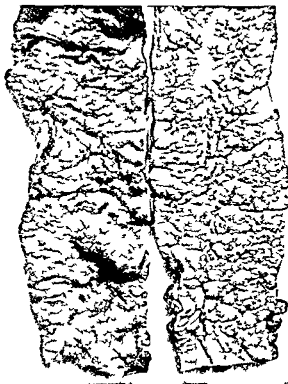


Fig 164 —Polypoid diphtheroid colitis

Although ulcerative lesions sometimes are found in the duodenum typhoid lesions in this part of the digestive tract are rarer than in the stomach Lesions are scant in the small intestine in the upper part as well as in the lower part of the jejunum They increase progressively in number and in size in the ileum as they approach the ileocecal valve since in this portion lymphatic formations known as Peyer s patches are more abundant

At autopsy of patients who have died of typhoid fever during the second or third week of the disease all of the successive stages of development of typhoid lesions can be seen These range from simple hyperemia and edematous enlargement of the small lymphatic follicles to confluent lesions with ulceration and hemorrhage Where the lesions are isolated they are found situ

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yellowish white areas of necrosis Occasionally large necrotic areas of infarcts may be observed in the spleen Histology is similar to that observed in the lymphatic glands

Liver—The liver is increased in size swollen of a reddish gray color sections appearing congested with necrotic areas which are not constant but which are uniformly distributed They cannot be seen easily macroscopically but can be seen readily in tissue sections The hepatic function is not greatly changed by the alterations in the liver The icterus sometimes observed in typhoid is due not to alteration of the hepatic cells but to changes in the cells of the reticulum and to changes in the biliary canals

Mallory and Wreed who made a thorough study of the focal alterations in the liver attributed these changes to thrombosis of the capillaries or to obstruction of the sinuses and compared this process to that which takes place in the glands One can observe in the liver the typical typhoidal granuloma with its great macrophagic activity and central necrosis

In the extrahepatic biliary passages constant lesions are acute cholecystitis chronic ulceration of the gall bladder and calculous cholecystitis It has been demonstrated in some gallstones that the center of the calculi had been formed by bacillary bodies Infection in the biliary canals and in the common duct gives rise to acute inflammation from which almost pure cultures of typhoid bacilli can be obtained by biliary drainage

Bones and Bone Marrow—In the course of the disease or sometimes months or years later periosteal lesions due to the typhoid bacillus occur often with no other manifestations of generalized infection There occur swelling and pain of the long bones (tibia femur) or of the vertebrae with later development of spondylitis A characteristic lesion is the periosteal abscess with intense advanced necrosis Rupture of the abscess causes a lesion of the bone which results in osseous caries extending to the bone marrow with eventual true typhoidal osteomyelitis

Cardiovascular System—In the heart typhoid causes degenerative lesions of the muscular fibers with phenomena of fibrillary fragmentation in the cardiac connective interstitial tissue hemorrhagic phenomena and thrombosis of the vessels are observed (myocarditis)

In the capillaries and veins the thrombotic lesions are due to accumulation of macrophages and precipitation of fibrin eventuating occasionally in complete occlusion Thrombosis independently of cellular obstruction is due to necrosis produced by the action of bacterial toxins upon the endothelium In the course of primary bacteriemia bacteria sometimes accumulate in the capillaries of the papillae of the skin and cause hyperemic reactions with accumulations of macrophages with resulting thrombosis this is typical of dermal lesions during the first week of typhoid (roseola typhosa)

Phlebitis is frequent in typhoid as demonstrated by splenic and pulmonary infarcts at times it may be fatal particularly when pulmonary emboli ensue

Trachea, Bronchi, and Lungs—Typhoid fever causes hemorrhagic tracheitis and bronchitis as well as hemorrhagic pneumonia in which many typhoid bacilli may be found

ted in the direction of the longitudinal axis of the intestine with a predilec on for lymphoid tissue The neighboring tissue of the intestinal wall is always dematous and enlarged sometimes double or triple the normal size Hyper mia of the affected area imparts an intensely red color to the intestine

Slight lesions involve the mucosa and submucosa More intense lesions rovoke different necrotic processes which extend beyond the closed follicles f the intestine to the entire intestinal wall In such cases areas are extremely ltered lymphatic and blood capillaries are blocked resulting in the necrosis f the whole intestinal wall in consequence the intestine perforates often ollowed by localized or general peritonitis

In the colon lesions are most numerous at the cecum and the ileocecal alve sometimes giving rise to pseudotumors which produce constipation or liarrhea Further along the cecum lesions decrease in number since this ortion of the intestine does not have a great quantity of lymphoid tissue Perforating lesions of the colon are very rare The appendix is always in olved and may be the site of extensive ulceration especially in the young ubject

Lymphatic glands of the mesentery are always involved in the typhoid process Beginning with those situated nearest the cecum (the normal area of drainage for the ileocecal segment) the mesenteric lymph glands undergo nflammatory changes showing some swelling and necrosis however not all glands situated in this area of drainage are involved

Rapid necrosis takes place in enlarged glands In those most affected here may be seen a change in appearance caused by hemorrhage and throm bosis Areas of various coloration yellow red gray and black may be ob erved Histologic examination reveals alterations in the structure of the glands The first changes seen are the proliferation of limiting cells of the sinuses and of the reticulum with formation of a large number of macro phages a situation similar to that described in the intestine

Examination of the glands of a patient who has died of typhoid shows that typhoid bacilli are not immediately found in great quantity but the number of bacilli is greatly increased in the glands a few hours after death In this process many macrophages are destroyed but new macrophagic cells replace them The germinal centers apparently disappear being replaced by pale masses of macrophages The gland cells as well as the periglandular tissue are affected proliferation of the reticulum and intense mononucleosis being noted If the glands undergo necrosis and the patient recovers these necrotic areas either cicatrize or are restored by tissue proliferation

Spleen—Splenomegaly is the most constant and characteristic finding in patients dying of typhoid fever This is due to the intense proliferation of the reticulum The same occurs in the mesenteric glands Intense blood regurgi tation of the splenic sinuses occurs The typhoid spleen is of a soft friable consistency intensely red in color with the capsule subject to great tension Sections show the pulp to be of a reddish gray color and containing a great quantity of splenic debris Malpighian corpuscles are easily distinguished sometimes appearing normal sometimes hypertrophic They are gray with

Hemogram.—The blood picture is *typical in typhoid fever in the child* according to observations in this hospital by Barreras. At the end of the first week, approximately the sixth day, the number of leucocytes is between 6,000 and 8,000 per c mm., occasionally from 4,000 to 5,000, with neutrophilia shift to the left, the "stab" count reaching 10 to 20 per cent, lymphopenia and disappearance of the eosinophiles. Before the sixth day the hemogram offers no special information except for an occasional slight leucocytosis and an increased number of "stabs." Leucocytosis (16,000 and higher) is found in the presence of pyogenic infections. The eosinophiles reappear during the final phase of the disease. They are important for the prognosis.

Blood Sedimentation.—Blood sedimentation tests are of value to estimate the intensity of the infection and in convalescence to determine when the child can return to his usual activity.

DIFFERENTIAL DIAGNOSIS

Paratyphoid Fever.—Identification of the bacterium by culture and use of specific sera permit an accurate diagnosis.

Acute Gastroenteritis.—Acute gastroenteritis may mark the beginning of typhoid fever. In gastroenteritis the number of stools is very numerous. The condition begins suddenly—this, however, may also be true of typhoid fever. There is no splenomegaly. Examination of the feces often shows Salmonellae or Shigellae. Blood culture and serologic reactions enable one to make an accurate diagnosis in cases of prolonged intestinal sepsis.

Influenza.—Influenza is characterized by a febrile process which frequently is not accompanied by respiratory manifestations. There is no splenomegaly. The disease has a short period of development. Laboratory examinations in prolonged forms of influenza are helpful.

Pneumonia.—Pneumonia can be confused with typhoid when the pneumonic process is deep and low and physical signs are absent. Cough, however, and changes in the respiratory rhythm, with the absence of abdominal symptoms, are valuable differential data. The hemogram will show an intense leucocytosis. Radiographs will present the characteristic Weil's triangle.

Typhobacillosis of Landouzy.—The clinical picture described by Landouzy almost always corresponds (Cardelle) with a primary tuberculous infection in infancy, especially after the second year of age. Prolonged fever, ballooning of the abdomen, mild splenomegaly, and coma point to a typhoid condition, especially when pulmonary manifestations are absent. An antecedent infection, a positive Mantoux test, and the finding of Mycobacteria, with negative Widal test, permit establishing the diagnosis.

There are no pulmonary signs in the first ten or fifteen days in Landouzy's disease in contrast to the early pulmonary congestion sometimes seen in typhoid fever, so that, paradoxically, pulmonary manifestations may be observed in the beginning of a typhoid fever.

Miliary Tuberculosis.—Miliary tuberculosis sometimes simulates typhoid. Biological tests, radiography, and blood examinations establish the diagnosis.

Genitourinary System—Most typical lesions of the genitourinary tract are focal lesions of the kidney (focal hemorrhagic nephritis)

Muscles—Interstitial hemorrhage is observed with Zenker type degeneration of the muscular fibers Lesions of the rectus abdominis major are very frequent

Brain and Meninges—Meningeal lesions are of two orders one caused by the toxin the other specific in typhoid fever in which McCollum has found the same alterations as in the primary lesions

SYMPTOMATOLOGY

Symptomatology is atypical in the nursling In the older child symptoms are similar to those in adults although milder

In children as in adults typhoid fever may present various clinical forms moderate benign or grave forms

Typhoid fever begins more or less insidiously in the child with a mild progressively rising fever and with few intestinal manifestations At times however and perhaps more frequently than in adults the disease begins with high fever convulsions and headache On one occasion we saw it begin with an acute gastroenteritis and anhydremia which led to a severe acidosis this case developed with extreme gravity and death followed in 80 days

Fever—The temperature reaches 39° or 40° C between the seventh and tenth days maintaining a plateau for 8 to 10 days then descending gradually by lysis in 4 to 6 days then returning to normal Altogether this requires 20 to 25 days so that on the whole the disease has a somewhat shorter and more benign development than in adults The fever generally is of the continuous type with slight morning remission 39° C and evening elevation 39 5° to 40° C progressively rising during the first week and stabilizing in 10 to 15 days A period of wide variations then begins 40° to 37 5° C 39 5° to 36° C etc for 4 to 5 days finally descending to normal or even to subnormal (hypothermic) temperatures for several days Naturally the fever curve may be modified by respiratory complications or complications of some other kind which frequently take place during an attack of typhoid fever

Circulatory Apparatus—Examination of the heart in a typical case does not reveal any changes of importance At times upon auscultation a functional blowing murmur may be heard especially when the temperature is very high Occasionally arrhythmia may be present Blood pressure is maintained within the normal limits if there are no complications

The pulse in infants follows the temperature in general in certain cases there may even be a slight tachycardia A pulse rate of 160 to 180 is not uncommon without the unfavorable prognosis which would be made under similar circumstances in the adult Exceptionally, bradycardia is observed but only in older children A dicrotic pulse is sometimes present but it is much less common than in adults

Respiratory Apparatus—In the majority of cases a mild cough begins on about the fifth or sixth day and auscultation shows rhonchi and sibilant rales proof of a mild bronchitis Occasionally bronchopneumonia occurs as a complication

Complications in the Respiratory Tract

Pulmonary congestion usually develops benignly during the early days of the disease

Bronchopneumonia —Bronchopneumonia is present later in the course of the disease or it may appear during convalescence The process develops with relapses and remissions in two or more weeks The prognosis is serious

Empyema —Empyema is almost always the consequence of a pulmonary complication due to bacteria other than typhoid bacilli

Complications in the Circulatory Apparatus

The most frequent complication is myocarditis which usually appears in the early period

Complications in the Digestive Apparatus

The complication most to be feared in the adult—intestinal perforation—is rarely seen in childhood

Perforation of the gall bladder may also occur in the course of an attack of typhoid fever it is accompanied by peritonitis More than 50 cases in children have been reported

Complications in the Nervous System

Aphasia has already been mentioned There may be other more severe complications meningitis hemiplegia due to cerebral emboli and very rarely polyneuritis We have observed polyneuritis only in patients on a prolonged typhoid diet we believe it is due to lack of vitamin B_1

PROGNOSIS

In children under 2 years of age the mortality is just as high as or higher than in adults after 2 years the mortality decreases and is lowest between the ages of 4 and 10 years When a good state of nutrition has been successfully maintained as with present methods of feeding the prognosis is much better than when patients are placed on needlessly prolonged diets Death at the present time generally occurs from complications myocarditis intestinal perforation encephalitis

*TREATMENT**

It can be clearly stated that despite progress in the diagnosis and prophylaxis of typhoid fever there is as yet no specific treatment for the disease Vaccines sera chemicotherapeutic procedures all remain useless The bacteriophage is too inconstant in its action to be relied upon The fundamental treatment of typhoid fever continues to be hygienic and dietetic

Hygienic and Dietetic Treatment

Bed Rest —Absolute rest in bed is one of the elements of good treatment Good nursing care will always be of great value

*See Chapter 29

Malaria—When a double parasitic cycle exists the fever is continuous and the general state is grave Definitive diagnosis can be established by finding Plasmodia in the blood

Brucellosis—In the child, brucellosis causes a prolonged fever of the undulant type accompanied by splenomegaly and at times by coma Serologic tests and blood cultures enable one to make the diagnosis

Meningitis—Typhoid fever may begin with a meningeal syndrome On the other hand purulent meningitis may begin with coma continuous fever, and splenomegaly Lumbar puncture is helpful

Other Infections—Other septic pictures may be mistaken for typhoid fever Some of these are acute appendicitis acute articular rheumatism osteomyelitis infectious mononucleosis pyelitis and acute endocarditis Close examination of the patient and laboratory tests will aid in making the correct diagnosis

CLINICAL FORMS

Mild Form

These forms common in nurslings are characterized by prolonged pyrexia without great disturbance in the general state At times a slight splenomegaly leads one to suspect *S typhosa* Development of the disease is short ten to twelve days The principal symptoms are absent In the case of every nursling or small child with an indeterminate pyrexia blood cultures should be made as well as the serologic tests for typhoid (Widal Welch and Stuart 1930) The disease does not always develop in a mild form We have seen several nurslings with the classical syndrome of the disease abdominal ballooning splenomegaly intestinal hemorrhage In such cases the prognosis is grave

Severe Forms

Prolonged Form—In some cases typhoid fever may be prolonged for 40 days 2 months or more as in our case of a 3½ year old girl who died after 83 days during which period all the usual complications of the disease were seen

Delirious Form—In this type the child presents nervous excitability with delirium and agitation The temperature is generally high the pulse is rapid It is relatively frequent in children 6 to 12 years of age

Ataxoadynamic Form—This is a form with great prostration which may result in coma There is a tendency toward hypothermia The pulse is weak Carphology is much less frequent in children than in adults

Hemorrhagic Form—In some patients there is a tendency toward hemorrhage sooty gums intestinal hemorrhage epistaxis petechiae

COMPLICATIONS

Typhoid complications are numerous Only those which are frequent can be mentioned in this chapter See Chapter 29

Intestinal Perforation —The only treatment for intestinal perforation is surgical This also applies to perforation of the gall bladder

Specific Treatment

Vaccination —Numerous attempts have been made to treat the disease by vaccine administration either subcutaneously or intravenously but these have not been satisfactory in practice (See also Chapter 29)

Serotherapy —From the first suggestions of Chantemese to the recent work of Schwartzman the proponents of this method have not as yet seen any results proportionate to their enthusiasm (See also Chapter 29)

Bacteriophage Treatment —*We have used bacteriophage treatment in* many cases and on two occasions have seen it bring about the crisis in very severe typhoid fever cases Until more is known about the adjustment of the typhoid bacillus to its bacteriophage this therapeutic measure must remain uncertain

Chemotherapy —Chemotherapy has not given us satisfactory results on the few occasions on which we have used it *

PROPHYLAXIS

The campaign against typhoid is launched by controlling drinking water drainage sewage food handling and carriers

Antityphoid Vaccination —The triple vaccine TAB contains per cubic centimeter 1 000 000 000 typhoid bacilli 750 000 000 paratyphoid A and 750 000 000 paratyphoid B It is given subcutaneously at intervals of 7 to 10 days in the following doses

Up to 2 years	0 2 to 0 4 c c
From 4 to 7 years	0 4 to 0 6 c c
After 7 years the dose is the same as for adults	0 5 1 0 and 1 0 c c

Nurslings less than 6 months of age are unsatisfactory antibody producers and vaccination at this time is usually not satisfactory For intradermal administration of the vaccine in children 3 doses are used 0 05 c c 0 1 c c and 0 1 c c This is the most satisfactory method according to Tuft and others (1941) of all the methods in use because the reaction is reduced to a minimum

SHIGELLOSIS IN CHILDREN

Dysentery is an acute intestinal infection It has been known since the time of Hippocrates †

The disease may occur at any age in the child It is more common during the first year than in the following years It is endemic in all countries especially in tropical regions In general it is more frequent in rural than in

*See Chapters 29 and 65
†See Chapter 29 and Gradwohl (1948)

Feeding—In nurslings breast feeding should be maintained throughout the course of the disease making exceptions according to general manifestations and temperature

If the child is older the necessary quantities of calories and vitamins and volume of liquids should be given taking account of the increased needs of the feverish patient

Adequate diet must be approached gradually dependent upon digestive tolerance A bland diet should be used preferably puree of strained vegetables meat or fish finely minced, eggs, milk, fruit juices or marmalades

A valuable addition to the typhoid diet is glucose and cereals flavored with maltose and vitamins particularly vitamin B_1 (10 mg daily) and vitamin C (100 to 200 mg, up to 500 mg daily) We have not seen serious nutritive alterations (edema typhoid polyneuritis hemorrhagic syndrome) in well fed patients

Blood plasma which brings protective elements as well as proteins and liquid to the patient seems to be indicated in dehydration or in grave forms of the disease The quantity to inject is 20 to 25 c c per kilogram of body weight If the patient is dehydrated liquids shall be administered orally hypodermically or by venoclysis A nursling requires on the average 150 c c of liquid per kilogram of weight daily in cases of severe intoxication more but special care should be taken not to exceed the necessary quantity in order to prevent production of a water balance disturbance

Symptomatic Therapeutics

Diarrhea—When diarrhea occurs give skimmed milk Feeding should be decreased until after the intestinal disturbance improves Antidiarrheal medicaments of the inert type may be used kaolin pectin or a diet of apples for 24 or 48 hours

Constipation—Laxatives of the mechanical type should be used with a base of mineral oil agar agar psyllium etc

Purgative Medication—Purgatives should never be used in typhoid fever

Hyperthermia—We are not particularly partial to antithermics of the chemical type (aspirin amidopyrin) although antithermic medication preferably aspirin may be used The best treatment of typhoid hyperthermia is hydrotherapy

Headaches and Nervous Manifestations—The best treatment is an icecap applied to the head

Myocarditis—Treatment of myocarditis can be summarized as absolute rest ice pack applied to the heart and strychnine Addition of vitamin B to the diet or by injection is useful

Intestinal Hemorrhage—Faced with the possibility of intestinal hemorrhage the following measures should be undertaken immediately

1 Liquid diet for the duration of symptoms
2 Ice bag applied to the abdomen
3 Opium (elixir of paregoric, laudanum etc)

The temperature varies In mild cases there may be slight febriculas or the patient may be apyretic Severe cases present marked hyperthermia with fever of 39° C according to the toxicity, followed by an algid state which may be prolonged for a longer or shorter period and which continues until recovery or death

Associated with bacillary dysentery there may be ocular lesions such as scleroconjunctivitis iritis cyclitis ulcer of the cornea serpiginous ulcer motor paralysis etc Another complication of bacillary dysentery is otitis media This was observed by Nedelson (1939) in 30 6 per cent of 153 patients

PATHOLOGIC ANATOMY

Salas found

Dysenteric bacillary colitis is present in children of a few months of age in the form of follicular ulcerative colitis in children 2 to 12

are changes in the capillaries with dilatation and desquamation of endothelial cells leading to capillary permeability with subsequent infiltration of the mucosa by blood cells

Phagocytosis may be due to metamorphosis of endothelial cells In the more advanced stage of the disease alteration occurs in the Lieberkuhn g l es place in the mucosal cells he submucosa is secondary to action of toxins or bacteria carried through the lymphatic or hematogenic routes

LABORATORY EXAMINATION

Etiologic diagnosis of this disease can be made only by bacteriologic examination of fecal matter Other laboratory findings however, are also important

Microscopic examination of the first feces reveals the presence of leucocytes erythrocytes and cells from the lining of the intestines usually mixed with clots of greenish mucus A few gram negative nonmotile bacilli are present Macroscopically the fecal matter is homogeneous in appearance with bloody spots and striations or a mucohemorrhagic clot At times the material is serosanguineous and often it contains portions of gangrenous mucosa (gangrenous form intensely fetid) Occasionally the material is purulent or mucopurulent having the appearance of pus from sputum or an abscess

In cases of intense dehydration there is lowering of the alkali reserve and acetone is present in the urine Urinalysis reveals moderate albuminuria with granular and hyaline casts erythrocytes and an increase in the number of leucocytes

Data gathered from hematologic studies (G Prado) reveal the following

1 Absence of anemia in 90 per cent of the cases This may be due to anhydremia usually seen in the patients

urban districts and is more prevalent in summer being endemic the rest of the year Outbreaks occur in asylums, nurseries hospitals and other institutions dedicated to child care

Mortality of shigellosis is generally greater during the first month of the child's life Clinical manifestations caused by the Shiga type are more severe than those due to the Flexner group The Shiga type causes the highest per centage of mortality from toxemia at any age in the child

In general, the incubation period of bacillary dysentery is short varying from 24 to 48 hours It may at times be as long as 3 to 6 days

CLINICAL PICTURE

Clinically the disease is divided into the so called acute form and the chronic or prolonged form The acute form includes mild forms or larvate dysentery and hypertoxic nervous algid typhoid gangrenous hemorrhagic and other forms

Aballi gave the following description of the clinical picture of the toxic form

The child apparently in normal health suddenly loses his appetite, and vomits Diarrheal manifestations of a fermentative type follow, becoming phlegmonous and finally mucohemorrhagic and changing from a nonfetid character to a final putrid state The picture is progressively intensified in relation to phenomena of intoxication until the death of the patient sometimes within 12 hours Most cases develop more slowly The intestinal symptoms may be accompanied by abdominal pain and intense tenesmus causing rectal prolapse

At times the vomiting is intense or persistent, aggravating the situation by dehydration The patient s abdomen may be boat shaped (acute development) or distended (rapid form) It is very painful to the touch and to palpation in the region of the ascending colon the cecum and the sigmoid region The pain may be constant causing the child to become restless and to complain continually

In the upper portion of the digestive tract there may be observed swollen gums dry lips and even crusts and bloody fissures—ulceration of cheeks and gums The tongue is moist it may be coated or desquamated

Hepatomegaly is present splenomegaly is absent

As to the respiratory apparatus slight bronchitic phenomena are observed in these cases as well as hyperplastic adenoiditis and tonsillitis.

In the circulatory apparatus there may be noted slow pulse from 80 to 90 maximum to 40 to 60 minimum according to age This 'slow down'' is very marked in severe cases and in the final stages which terminate in rectal prolapse Cardiac tone is weakened There is generally observed no alteration of rhythm and no car liac souffle

Symptomatology of the nervous system is exhaustion and indifference to surroundings in severe cases typhous aspect with hallucinatory phe nomena at times. Cutaneous and tendonous reflexes are diminished

panied by encephalitis The property of producing exotoxins is not constant in the Flexner and Sonne types, and this may perhaps account for the uselessness of the serum in certain clinical conditions due to these organisms

At the Children's Municipal Hospital of Havana, García Montes, Silva, and O Fernandez used the Flexner antidysentery serum successfully in a series of 16 cases They employed 2 or 3 doses of 20 c c in 24 hours, continuing to use it daily until cessation of acute intestinal symptoms and toxemias were obtained

In commenting upon the practical importance of treatment of Shigellosis by sulfonamide drugs we shall discuss the subject according to the findings by Castellaños (1945) Since shigellosis is a disease of the digestive tract, sulfonamide drugs which act on intestinal lesions should offer the best results such as sulfaguanidine and sulfasuxidine These are toxic to a lesser degree and are more readily tolerated and more innocuous than the soluble sulfonamides Some investigators such as Cooper, Zucker, and Wagoner (1941), Halper and Cunningham, Yannet, Leiboitz and Deuth, Tudor, Hardy and Watt (1942), Scroggie Manchaca (1941), Zerbino (1942), etc, have demonstrated that there is no difference in the treatment of bacillary dysentery in the child with one type of sulfonamide or another

Some dysentery bacilli are more resistant to sulfonamides than others According to Hardy and Watt the *sonne* infection is of this type

Although sulfaguanidine and sulfasuxidine are the drugs of choice in shigellosis in cases of diarrhea of unknown etiology where the bacteriologic report might be delayed, it is well to follow the suggestions of certain South American pediatricians (Scrogie, Zerbino, Peluffo, Aleppo, Menchaca etc) to begin treatment of infantile diarrhea with a soluble drug such as sulfathiazole or sulfadiazine Other pediatricians prefer to begin the treatment with sulfaguanidine or sulfasuxidine for 48 to 72 hours If the patient improves he is kept on these drugs without resorting to the soluble forms (sulfathiazole or sulfadiazine)

According to Cooper, in refractory cases of shigellosis, rotation of the sulfonamides at times shows good results Castellaños insists that in Cuba there are many refractory cases of shigellosis which can be overcome by rotation of the sulfonamides, but that sometimes sulfonamide therapy is of no value Such cases according to Castellaños, can be treated by autogenous vaccines (oral and by injection)

Al alli and Castellaños have directed attention in Cuba to the possibility that there may be certain species of Shigella resistant to sulfonamides which have been developed by use of small and continuous doses of the drug

The dosage recommended by Castellaños for the treatment of shigellosis by sulfonamides is

Sulfasuxidine Initial dosage of 0 25 Gm per kilogram of body weight, then 0 25 Gm per kilogram per day, divided into six equal doses In a severe case the initial dose may be omitted and one tablet every four hours should be used day and night

2 Neutrophilia and left nuclear shift present in all cases, myelocytes present in 40 per cent

3 Absence of eosinophilia lymphocytosis and a marked increase in irritation cells

4 Monocytosis as high as 20 per cent, present in a large percentage of cases

5 Nuclear changes (basic chromatin) and alterations of the cytoplasm of the neutrophiles (toxic granules) are always present In serious cases toxic granules may be found in all neutrophiles

6 The bone marrow shows the infectious pattern

Infection is localized in the intestine, and for this reason blood cultures remain constantly negative It is only in very severe cases that these may be positive Only eighteen cases of septicemia due to dysentery bacilli have been reported in medical literature

Diagnosis is usually made by isolating the bacteria from fecal material that is by bacteriologic examination which is the sole means of determining the nature of the disease

Serologic Tests

Macroscopic agglutination methods are used Interpretation of results is difficult since children suffering from dysentery have agglutinins for different types of Shigella Only the following titers or higher titers are of positive value Shiga 1 50 Flexner 1 200 and Sonne 1 150 When a serum shows agglutinins simultaneously for different Shigellae the species which agglutinates at the highest dilution is probably the cause of the infection

TREATMENT

General treatment recommended by Aballi consists in combating the anhydremia and the intoxication by administration of water and electrolytes Opium in the form of a tincture gives good results This may be associated with bismuth and tannin (albumin tannate acetyltannic acid) In prolonged cases autogenous vaccines may be used but although they have proved useful for some investigators others have denied their value

There is no agreement among authorities with respect to the diet for children with dysentery A liquid diet for 12 to 48 hours varying with the toxic state of the patient gives good results Re alimentation should begin with defatted lactic acid milk Patients must be given vigilant care during this period for they may lack tolerance for carbohydrates in which case they must receive an added quantity of proteins This addition may be made advantageously by means of Casec (*Mead Johnson*), or by using the albumin milk of Finkelstein

German authors especially have shown the advantages of treatment of bacillary dysentery with the apple diet (Moro)

Felsen (1939) recommended neutralization of specific toxins by appropriate sera and established the fact that dysenteric serum is of value during the first 24 to 48 hours If no useful results are obtained he recommended using immune blood According to Seidlmayer (1939), the serum is beneficial in cases accom

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Sulfaguanidine Initial dosage 0 10 Gm per kilogram of weight, then 0 05 Gm per kilogram of weight Two tablets to be taken as initial dose followed by one tablet every four hours

Sulfadiazine In severe cases the initial dose is from 0 05 Gm to 0 10 Gm per kilogram of weight then 0 20 Gm per kilogram of weight within 24 hours or one may be taken every 4 hours 6 times a day, 2 5 cg per kilogram in each dose Teverett and Nelson recommend half of this dosage

Sulfathiazole In severe cases initial dose is 0 10 Gm per kilogram of weight then treatment to be maintained on the basis of 0 20 Gm per kilogram per day or 0 03 Gm per kilogram of weight in each dose to be taken every 4 hours *

Sulfonamide dosage may be increased or decreased according to the intensity of the clinical picture and depending upon the tolerance of the patient so that a set quantity cannot be maintained

The dosage recommended above is to be maintained while the symptoms are present With improvement in intestinal movements and disappearance of the fever improvement in hydration doses may be taken at 6 hour intervals In severe cases according to Castellaños sulfonamides should be taken for 6 to 8 days even though the clinical condition of the patient is very satisfactory In less severe cases the time may be reduced to 4 days never less

Aballi Jr gives the figures (Table XVIII) of results obtained in the treatment of 74 cases of shigellosis

TABLE XVIII

	CASES	GOOD RESULTS	NO RESULTS	PER CENT OF FAILURES
Sulfaguanidine	54	39	[illegible]	[illegible]
Sulfasuxidine	10	6	4	40
Other sulfonamides	10	6	4	40

PROPHYLAXIS

Contamination by bacillary dysentery is proportional to the conditions of sanitation in the community and to personal hygiene See also Chapter 29

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CHAPTER 31

LEPROSY

V. PARDO CASTELLÓ

Leprosy may be defined as a chronic infectious and contagious disease, caused by *Mycobacterium leprae*, presenting periods of quiescence and activity, which preferably affects the skin and peripheral nerves but which may also affect the internal organs of the human body to a greater or lesser extent.

Leprosy is widespread throughout the world. Its prevalence is in inverse proportion to the standard of living of a community. Leprosy is prevalent in backward poverty stricken, filthy centers of human aggregations. However, even among the cleanest, most sanitary, and healthiest peoples, some cases of leprosy are found. China, Indo China, India, Japan, and the South Sea Islands are the greatest leprosy foci. In the Americas, Brazil and Colombia have the largest number of cases, with the Antilles, Mexico, Argentina, and other South American countries following. It is said that there are about 5,000 lepers in Cuba, but only about 2,500 are known to and supervised by the sanitary authorities. In the United States, leprosy is endemic along the coast of the Gulf of Mexico, from Key West to Texas, on the west coast a number of cases are discovered each year, and along the Atlantic seaboard a smaller number is also diagnosed. In New York City there are a number of patients with leprosy at large, since the State of New York has no provision for isolating or otherwise restraining these patients. Most cases in the United States are sent to the National Leprosarium in Carville, La., a model institution, with a total of about 300 patients. In Cuba there are 2 leprosaria, housing about 600 patients, and an official body under the Ministry of Health supporting 10 ambulatory or dispensary centers for the diagnosis of leprosy.

In Europe, leprosy is endemic in certain provinces of Spain and Italy, and a number of cases are found in France, England, and in the Balkans. In Russia and the Near East, leprosy is rather prevalent, especially in Turkey and Asia Minor. Sweden and Norway, which were endemic centers of leprosy during the nineteenth and the early part of the twentieth century, have succeeded in eradicating the disease in the last twenty five years.

Leprosy affects both sexes and all races, but men are more often the victims of this disease than women. The first symptoms are usually seen in early youth, although children and old people may also acquire the disease. One of the earliest cases seen by the author was of a child who had acquired the disease from the midwife and who presented the first symptoms of leprosy at the age of 4 months. In endemic areas, children are considered more susceptible to the infection than adults.

Leprosy is not hereditary nor has a single authenticated case of congenital leprosy ever been reported. Children born of leprous mothers remain

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unsatisfactory classification into cutaneous, neural, and mixed types The works of Rabello (1936), Sousa Lima (1938), Schujman (1940), and others in Brazil, and of Baliña and Basombrio (1938), Fernandez (1942), Basombrio (1943), and others in Argentina should be consulted by those interested in the details of these most excellent contributions to the knowledge and understanding of leprosy The author presented a résumé of the subject in 1942 (Pardo Castello, 1943) before the annual meeting of the American Medical Association

The *nodular* or *lepromatous type* shows diffuse infiltration of the dermal and hypodermal tissues It is a granulomatous infiltration composed of numerous large vacuolated badly staining foam cells loaded with hundreds of acid fast bacilli (Virchow s "Leprazellen") and many lymphocytes and plasma cells This type of pathologic change occurs in those tissues that have poor defense and allow an easy and rapid invasion of the specific agent and is therefore typical of the serious and severe forms of leprosy

The *simple inflammatory tissue reaction* is seen in many early cases of leprosy characterized by lymphocytic perivascular periglandular, and perifollicular infiltration vascular dilatation and congestion and edema This type of cellular reaction is seen in recently infected cases where insufficient time has elapsed for proper defense development or for the surrender of the tissues to the invader In time, this type changes into the lepromatous or the tuberculoid type

In the *tuberculoid type* the cellular infiltration is characteristic it occurs in the form of well defined masses situated in the whole of the dermis, usually beginning around the blood vessels, glands and hair follicles, sometimes in the form of cellular nests sausage shaped or oval collections composed of lymphocytes large foam cells, and multinucleated giant cells resembling the infiltrate of the tuberculids or, better, that of sarcoidosis This type is seen in patients whose tissues have adequate defenses against the specific agent as stated in the law of Jadassohn and Lewandowsky (quoted by Sulzberger, 1940) In these tissues it is very difficult to find the Hansen bacillus, which may be seen occasionally embedded in the giant cells never in the large numbers seen in lepromatous tissues Tuberculoid leprosy occurs therefore as a benign type of the disease, with a chronic, usually nonmutilating course at times with spontaneous regression and cure

The simple inflammatory type is usually transitory and in due time changes either to the lepromatous or to the tuberculoid type, but once the type is established it remains so for the duration of the life of the patient except in very exceptional cases still the subject of dispute by leprologists Most leprologists state and the author is in accord with them, that a tuberculoid type never changes into a lepromatous type, but occasionally a lepromatous type may develop adequate defenses and change into the tuberculoid or more benign type This latter occurrence is very rare In any case the presence of lepromatous lesions under the microscope brands the case as definitely "lepromatous" regardless of the simple inflammatory structure of other

healthy and develop normally if removed from their environment Climate and food have no relationship to leprosy This disease is not a tropical condition, although it is common in the tropics it is also frequent in the coldest climates such as Russia as it was in Scandinavia It is a disease which is prevalent among the poorest classes among those who live in crowded quarters and under unsanitary conditions

Leprosy has never been successfully inoculated into lower animals although a similar disease has been described in the rat it is generally conceded that this disease is not the same as that which affects the human being Transmission of leprosy to the hamster has also been reported but so far these experiments have not been corroborated

ETIOLOGY

Leprosy is caused by *Mycobacterium leprae* known as the Hansen bacillus an acid fast organism which up to the present time has remained uncultivated This is a short bacillus with fine ends staining red with Ziehl Neelsen s method and resembling the bacillus of tuberculosis It may be differentiated from the tubercle bacillus because it is usually grouped in masses held together by mucus or at least in cigar like bundles These bacilli are easily found in most cases of leprosy in the mucous membranes of the nose in the lymph which oozes from superficial erosions of the skin or better still in the scrapings of the corium after a superficial cut or after curetting of the epidermis They are usually found in huge numbers in tissue sections of the lepromatous types of leprosy The round or oval masses of bacilli apparently held together by a mucoid substance are called *globi* The bacilli may be found also in the peripheral nerves as well as in the liver and other viscera in advanced cases of leprosy

It is not known whether *Myco leprae* may live outside the human tissues The actual mode of contagion is also obscure although it is assumed in the majority of cases that prolonged personal contact with the patient must exist before the disease is acquired Direct inoculation on the skin with development of an initial lesion has been reported by some observers but it is also generally accepted that the disease may have access to man through the mucous membranes of the nose and mouth

Inoculations of human beings have not been successfully performed although few doubt that it is possible in susceptible individuals

PATHOLOGY AND IMMUNOLOGY

The tissues attacked by *Myco leprae* react in general first in an indeterminate simple inflammatory way and later when the tissues have been in prolonged contact with the specific agent in a nodular or lepromatous type or in a tuberculoid type This has been the basis of the newer classification of the forms of leprosy by the South American school of leprologists We believe the new classification should be universally adopted with elimination of the older

In individuals who have never been in contact with lepers the Mitsuda tes is also positive in the majority of cases

In the early macular type of leprosy corresponding to the simple inflammatory type the observer may predict the future of the patient accordin to the results of the Mitsuda test If the test is negative the patient will develop a lepromatous case with all the severe manifestations of leprosy If however the Mitsuda test is positive it may be safely predicted that the patien will develop a tuberculoid type of leprosy with the usual benign evolution o such type

SYMPTOMATOLOGY

The incubation period of leprosy may be very long in some cases 10 and even 20 years Again it may be rather short a few weeks or a few months In the majority of cases it is impossible to ascertain the infective contact and therefore the time of incubation remains unknown

Leprosy may begin insidiously taking months and even years to develop a few symptoms but it also may start with an acute attack In the first case the phenomena observed are successively as follows rhinitis with profuse mucous discharge or crust formation which makes breathing through the nose difficult epistaxis cutaneous and neural symptoms such as macules nodules disturbances of pigmentation areas of anesthesia and paresthesia especially along the ulnar region of the forearm atrophy of the small muscles of the hands loss of sensation to temperature and pain in the extremities with the development of bullae swelling of the dorsa of the hands loss of hair on the outer half of the eyebrows atrophy of the skin with scaliness reabsorption of the phalanges mal perforans plantaris and other symptoms to be described later

When leprosy begins in the form of an acute attack the patient apparently healthy until a few hours before suddenly develops chills and fever peripheral aches and pains headache arthritis and on the skin a macular or maculonodular eruption with the symptom complex of erythema multiforme or erythema nodosum The diagnosis may be quite difficult and often the case is diagnosed as erythema multiforme of the allergic or infectious (streptococcus) type This acute stage may last for several days or weeks while the patient becomes emaciated Often the condition regresses and a few permanent lesions remain together with beginning atrophy of the muscles of the extremities During this period the erythrocytic sedimentation test may be extremely accelerated as high as 150 millimeters in one hour The number of Hansen bacilli in the skin and in the capillary blood is enormous

When the contacts of a patient with leprosy are examined one often finds one or two such contacts suffering from leprosy of the simple inflammatory or the tuberculoid type quite unknown to the patient These cases show a few macular lesions or one or two infiltrations with few if any bacilli but with the typical disturbances of sensations which characterize these lesions of leprosy Very often only an area of anesthesia is found without apparent discoloration or change in pigmentation

lesions equally the presence of a tuberculoid structure brands the case as "tuberculoid" even if the majority of other skin biopsies demonstrate simple inflammatory reaction

THE LEPROMIN TEST (MITSUDA TEST)

The antigen for the lepromin test is made with tissue rich in *Myco leprae* and is called *lepromin* Although Rost (cited by Jeanselme) as long ago as 1907 made an antigen from a suspension of Hansen's bacilli the application of such antigen to the study of immunity in leprosy was first published by Mitsuda (1924) in 1916 Little attention was paid to his work until the International Congress of Leprologists met in Copenhagen in 1923

The value of the test lies in the fact that an intradermal injection of minute quantities of lepromin antigen produces a definite allergic reaction in certain patients with leprosy while it elicits no reaction at all in others

The test is made by injecting 0 1 to 0 15 c c of lepromin intradermally either into the skin of the scapular region or upon the anterior surface of the thigh above the knee Any other location may be used but Fernández (1942) advises the scapular region because it is usually devoid of hair it is out of the reach of the fingers and is away from the curious eyes of the patient

At the end of 24 to 48 hours there is a light erythema which is attributed to the presence of foreign protein material and which disappears in a few days usually 3 to 4 The site of the test then remains apparently normal until the beginning of the third week when if the test is positive a slight papular infiltration is noted gradually increasing in size until it attains the size of a pea The infiltration is deep in the dermis and the color is bright red There may be some tenderness on pressure and occasionally formation of a central focus of necrosis with ulceration causing a permanent scar

The Mitsuda test is positive in about 90 per cent of normal individuals in practically all cases of tuberculoid leprosy and in about 50 per cent of patients presenting the simple inflammatory type which is characterized by the presence of macular lesions It is negative in practically every case of lepromatous leprosy in about 10 per cent of apparently normal persons and in about 50 per cent of patients with the simple inflammatory type of leprosy

The Mitsuda test is not a diagnostic procedure for leprosy It serves the very useful purpose of determining the defenses of the subject and therefore shows the resistance of the patient to the invasion of the *Myco leprae* *It is therefore a prognostic test* When it is negative the patient shows no defenses and is an easy prey or victim of the disease When it is positive it shows that the subject possesses adequate defenses against the *Myco leprae* and that therefore if he is already affected he will suffer from a mild case and may live without the mutilations and deformities of the severe lepromatous type of leprosy When the Mitsuda test is negative in a person without symptoms of leprosy it shows that the person is susceptible to the disease and therefore should avoid contact with lepers This test is applied to all prospective employees of leprosaria and those with negative Mitsuda tests are not allowed to serve in such institutions

varying in size from that of a millet seed to that of a tomato that is from a few millimeters to several centimeters in diameter The color is deep red dark red or purplish according to location and duration The surface is smooth and shiny in the majority of cases with dilated pilosebaceous follicles sometimes filled with inspissated sebaceous material As a leproma ages the skin becomes wrinkled and scaly resembling senile skin

Lepromas may appear on an apparently healthy skin or on a previously existing macular lesion and may be so numerous as to cover the whole surface of the body but even in the most profuse cases the scalp the flexures the inguinocrural regions and the temporal regions are usually free of lesions The earliest affected parts are the lobes of the ears the eyebrows the fore head the nose the chin and the extensor surface of the extremities especially the elbows and knees Often the lesions are symmetrically situated



Fig 165 —Typical lepromatous facies (Courtesy of Raul Piñeyro)

When they occur on the face the lepromas deform the features of the patient the ears are serrated or grossly lobulated and the lobes of the ear are often studded with deep seated shot like infiltrations When lepromas are numerous on the face the patient presents a cruel and brutish appearance which has been known for a long time under the inappropriate name of *leonine facies*

Lepromas may also present a diffuse appearance in the form of plaques of varying size usually several centimeters in diameter, flat and with in distinct borders At times these plaques are so extensive as to cover large areas of skin They are a variegated color in which deep red pink dark red and purplish mix and intermingle The surface may be smooth wrinkled or scaly according to the time of evolution These are called lep romas "en nappe "

THE CLINICAL FORMS OF LEPROSY

The three fundamental types of leprosy, lepromatous, tuberculoid and simple inflammatory, may affect the skin, the peripheral nervous system and also the eyes, the larynx, the mammary and sexual glands and the viscera. We shall describe in succession the symptoms of leprosy in the skin, in the peripheral nerves and in the other organs mentioned. These histopathologic types correspond to fairly well defined clinical types and may be diagnosed on clinical inspection by the experienced physician. As in many other conditions there are exceptions to this rule and at times even the most experienced diagnostician must wait for a pathologic report before expressing a definite opinion concerning the type of leprosy in a particular case.

The correlation of the clinical *manifestations* of leprosy with the histopathologic changes, the immunologic response and the bacteriologic findings may be better expressed in Table XIX.

TABLE XIX

CLINICAL	PATHOLOGY	IMMUNOLOGY	BACTERIOLOGY
Lepromatous Nodules, lepromas, diffuse infiltration, enlarged lobes, loss of eyebrows, rhinitis, leonine facies, fever and peripheral pains. Mutilations: Nose, extremities	Diffuse infiltration of dermis of foam cells, Leprazellen, with globi. Atrophy of the epidermis. Atrophy of hair follicles and glands. Areas of necrosis	Mitsuda test negative in 90 per cent	Skin: Many bacilli singly, in bundles and globi in sections and capillary blood. Nerves: Numerous bacilli singly and in bundles in and between nerve fibers in sections
Tuberculoid Flat [illegible] tions [illegible] graphi[illegible] [illegible] nerves [illegible] fever [illegible] atrophy of hands. Includes the old neural types	[illegible] no globi. Nerves: [illegible] fuse infiltration, same type	[illegible] test positive in 90 per [illegible]	Skin: Occasional bacilli in sections. Nerves: Occasional bacilli in sections
Simple Inflammatory Macular lesions with little or no elevation, pink, red or leukoderma, areas of anesthesia without clinical changes	Lymphocytic infiltration around blood vessels, glands and hair follicles. No foam or giant cells, no globi	Mitsuda test positive in [illegible] to 40 per cent, negative in [illegible] to 60 per cent	No bacilli or only occasional in sections

The occurrence of simple inflammatory or tuberculoid lesions of the internal organs is questionable since only the lepromatous cases in the advanced periods of the disease show certain visceral changes. It is rather improbable that the early manifestations of leprosy consisting of simple nonspecific inflammation and the benign tuberculoid manifestations of this disease affect the internal organs.

Leprosy of the Skin and Mucous Membranes

The most common and typical lesion is the *leproma*, a circumscribed, elevated, prominent nodule affecting the dermis and subcutaneous tissue and

coalesce and form geographic figures When several lesions of different duration coexist the skin takes on a peculiar variegated appearance

The pigmented macules are frequently an end result of the evolution of erythematous changes but often primarily pigmented macules appear too They are round oval irregular patches of slaty brown or chocolate color and often intermingle with the erythematous and achromic lesions The purely pigmented macules of leprosy affect the trunk and extremities but are much less common than the erythematous

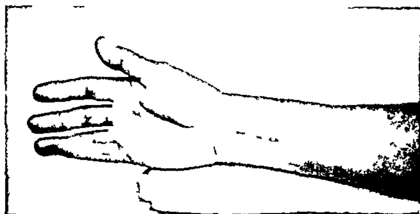


Fig 166—Early simple inflammatory lesion of leprosy A solitary anesthetic erythematous manifestation



Fig 167 Lepromatous manifestations with destruction of the septum of the nose (Courtesy of Raul Piñeyro)

The achromic or leucodermic spots or macules of leprosy often form a halo around the pigmented or the erythematous macules The color is not as white as that of the vitiligo lesions but rather ashy and they are never scaly Often the order is reversed and the achromic spots are surrounded by an erythematous or a pigmented ring *These dyschromic* lesions were known formerly as *vitiligo gravior* and also as *morphea alba gravis*

Lepromas may remain unchanged for a long time several months or years but often they undergo a softening process becoming necrotic and break down to form ulcers with undermined edges dirty purulent floors and foul secretion These ulcers finally heal leaving depigmented or pigmented irregular scars at times atrophic and scaly After attaining a certain size some lepromas begin to recede and finally are reabsorbed without ulceration and disappear leaving depressed scars covered by wrinkled and scaly epidermis The ulcers caused by these lepromas are very slow in healing an easy prey to secondary infection and when situated in the fingers and toes may cause opening of the joints and loss of the phalanges All of these lesions are usually completely painless

The mucous membranes may also be the site of lepromas especially those of the nose Rhinitis is one of the earliest manifestations of leprosy This rhinitis begins in the form of a chronic catarrh with crust formation snuffles continuous secretion of mucus and occasional epistaxis Later the septum of the nose ulcerates the secretion becomes abundant purulent and offensive the nose sinks producing the shape of a saddle or of the so called telescopic deformity that is the lower part of the nose seems embedded in the upper part The mucus contains an enormous amount of Hansen bacilli The palate and the nasopharynx may also be the site of lepromas In the final stage the hard palate breaks down the bone is eliminated in the form of splinters and an opening occurs between the floor of the nose and the mouth water and food escape through this opening The tongue may show chronic glossitis being lobulated fissured and studded with lepromatous nodules Lepromas localized in the larynx are particularly dangerous The voice becomes husky then whispered finally the infiltration of the vocal cords and of the glottis and epiglottis may make intubation imperative if possible or the urgent performance of a tracheotomy

The *simple nonspecific inflammatory* lesions of the early cases of leprosy frequently found in contacts with a certain patient consist of macules of three types erythematous leucodermic and pigmented These lesions usually exist in small numbers at times there are only one or two of them and occasionally they are very numerous

The erythematous macules are the most common and are also observed during acute exacerbations They vary in size from a few millimeters to several centimeters and at times may cover extensive areas of the skin surface usually by the confluence of various smaller lesions The outline is round or oval at times they tend to clear up in the center to form ring like or crescent shapes or they may form circinate or geographic lesions These hyperemic macules are at first smooth but later they may show a furfuraceous type of scales and present a powdery aspect Sometimes these scales are so abundant and imbricated that they resemble the lesions of psoriasis

The color of these erythematous lesions is pink or light red at first but as they grow older they become purplish and at times take a salmon or sepia hue The outlines of the individual lesions are fairly regular and well delineated from the surrounding skin Two or more areas of erythema may



Fig 169—Gynecomastia in a man with lepromatous leprosy (Courtesy of Raul Piñeyro)



Fig 170—Tuberculoid leprosy flat nodules of the skin

Of all these lesions the erythematous are the most common the achromic are rare and the pigmented still rarer

All of these lesions have a common character with disturbances in sensations invariably present in all There is absence of sensation to pain and to temperature but as a rule, the sensation of touch is preserved The touch sensation may be lost in advanced cases

All the macular lesions of leprosy are known by the common term *leprids*

The *tuberculoid* lesions of the skin are usually observed in a pure state but occasionally are combined with the macular lesions described above The diagnosis of this type of leprosy may be difficult but it is possible with the aid of clinical examination by an expert who has seen many cases of leprosy



Fig 168 —Alopecia in a case of lepromatous type of leprosy (Courtesy of Raul Piñeyro)

However the clinical diagnosis should be confirmed by pathologic examinations whenever possible The cutaneous lesions of tuberculoid leprosy are small nodules of the size of a pinhead purplish disseminated or grouped slightly prominent resembling patches of lupus vulgaris or of miliary sarcoid perifollicular papules of lichenoid type resembling the lesions of lichen scrofulosorum dermo-hypodermic nodules the size of a filbert or even larger few in number with a deep red or purplish surface frequently located on the extremities where sometimes they resemble the lesions of erythema induratum of Bazin flat plaques round or oval in outline serpiginous or capriciously outlined covering from several centimeters to large areas of skin especially on the trunk with their centers slightly depressed lighter in color sometimes scaly and the edges well raised covered with papular elevations achromic lenticular lesions or plaques with round oval or irregular outline and with little infiltration in the surrounding skin

These manifestations of tuberculoid leprosy are also anesthetic usually more so in the center than on the periphery

studded with globi and the nerve fibers show progressive degeneration there is not much cellular infiltration or focal inflammation In the tuberculoid types on the contrary the nerves show few if any lepra bacilli but the nerve tissue is greatly invaded by the presence of typical tuberculoid cellular infiltrations composed of lymphocytes epithelioid cells and often giant cells of the Langhans type These cells are grouped in masses resembling the foci as seen in the same type of lesions in the skin A particular type of tuberculoid leprosy of the nerves ends in necrosis causing the formation of a collection of necrotic material with the appearance of pus which adheres to the skin resembling an abscess finally opening and leaving a small ulcer This type of neuritis has been described as *neuritis nodular colliquativa* by Rabello of Rio de Janeiro (1932)

The Trophic Disturbances in Leprosy

The trophic disturbances which are the result of peripheral neuritis described above may be discrete or very numerous according to the individual case They are usually less frequent in early cases and more severe and numerous in advanced cases The tuberculoid types of leprosy may show some of these disturbances rather early in the disease while the lepromatous cases may not present them until the most advanced stage Early manifestations of the lepromatous types are bullae on the bony prominences such as the elbows knees and the knuckles localized gangrenous patches on the hands and feet and painless ulcers usually on the soles especially on the head of the first metatarsal bone or elsewhere on the feet The bullae usually develop suddenly break open or they may dry without breaking and recur repeatedly on the same sites causing extreme atrophy of the skin and even atonic ulcers and finally depigmented atrophic scars The ulcers may also be the result of the breaking down of the lepromas or of localized areas of necrosis and gangrene On the fingers and toes these atonic ulcers foul and bleeding secreting yellowish green pus usually completely painless may open the finger joints and cause mutilation by loss of the phalanges The fingers fall off in pieces without the least pain Secondary infection may cause chronic lymphangitis which is seen along the extremities in the form of dark brown ascending streaks On the feet these mutilations often begin in the form of mal perforans plantaris common in both lepromatous and tuberculoid cases these are located on the head of the first and of the fifth metatarsal bones on the base of the toes or on the calcaneus These are deep ulcers funnel shaped with callous borders reaching deeply into the skeletal parts and destroying them so that sequestra are very frequently expelled through the ulcers without any pain These patients walk with scarcely any difficulty on infected bleeding feet sometimes almost reduced to stumps

As to the skin glands certain disturbances are also observed especially hyperhydrosis The lepra patient perspires freely and soaks his clothes sometimes without exertion especially in the early stages of the disease Later this phenomenon becomes less marked and the sweat secretion may be greatly decreased in the more advanced stages The sebaceous secretion increases

These lesions of tuberculoid leprosy may be difficult to differentiate from those of the simple inflammatory type when the lesions are beginning to change Then the pathologic diagnosis must serve as the deciding factor

Leprosy of the Nerves

Myco leprae attacks the peripheral nerves causing neuritis usually symmetrically The large nerve trunks are either uniformly thickened or present nodular enlargements resembling beads The nerves most frequently affected are the ulnars which may be palpated behind the elbows along the epitrochlear canal the auricular branch of the superficial cervical plexus which may be felt or seen across the sternocleidomastoid muscle the popliteals the peroneals and less frequently the radial and median nerves This polyneuritis may cause intense pain but as a rule the nerve is destroyed and as a result the skin of the affected parts becomes anesthetic The cranial nerves are often affected too especially the facials and the oculomotors

It is generally accepted that this neuritis progresses centripetally at times reaching the spinal roots to cause radiculitis very rarely myelitis has been reported *Myco leprae* seems to invade the skin nerve endings first, the bacilli ascending along the nerve trunks causing their gradual degeneration

Leprous neuritis causes excruciating pains with paroxysmal exacerbations in some patients particularly in the tuberculoid type of the disease which is often confined to the nerves with almost complete absence of cutaneous manifestations Hyperesthesia and burning sensations are also experienced by some patients Later after the nerves have degenerated anesthesia is the persistent phenomenon throughout the life of the patient These zones of anesthesia are usually in the form of bands along the extremities beginning along the ulnar border of the hands and forearms and later spreading to the entire upper extremities Pain and thermal sensations are first affected with the result that the patients suffer burns without noticing them while smoking cooking or leaning against a stove At times the first indication to the patient is the smell of burning flesh The sensation of touch persists unaffected for the longest period and is lost only when the disease reaches its most advanced stages Then the leper cannot pick up a pin or button his clothes without a great deal of difficulty The touch of a feather or of a flake of cotton on the affected parts is not noticed by the patient

This neuritis is also present in all the macular and nodular lesions of leprosy to a greater or lesser degree so that this sign becomes one of the most typical of the disease and serves to identify it in cases when the diagnosis is in doubt

When neuritis is of long standing the complete degeneration of the nerve trunks causes trophic disturbances paralysis muscular atrophies, retractions and deformities of the fingers and toes ulcers and gangrene

Leprous neuritis is an interstitial neuritis in cases of lepromatous leprosy the large nerves being invaded by enormous amounts of lepra bacilli without much defensive reaction The nerves are filled with bundles of bacilli or

placed by scar tissue or may be entirely absent the finger or toe showing a necrotic ulceration instead One of the earliest manifestations observed in the lepromatous type of the disease is the *gable nail of leprosy* described by Pardo Castello (1946) The free edge of the nail is indented and the outer surface of the nail presents a ridge longitudinal to the posterior wall of the nail the whole resembling a gabled roof Diffusion of the lunula over the posterior two thirds of the nail is an early phenomenon in cases of lepromatous leprosy



Fig 17 —Tuberculoid leprosy Enlargement of the auricular branch of the superficial cervical plexus

The muscles are affected early in cases of tuberculoid leprosy and may be equally although not as extensively atrophied in lepromatous cases The first symptoms are present *in the small muscles of the hands* the *interosseous* muscles and the muscles of the thenar and hypothenar regions the hands being thin atrophic the fingers retracted and the palms flat and even Sometimes the line of the heads of the metacarpal bones forms a prominence across and the retracted fingers seem to clench the palm The movements of opposition of the thumb are greatly limited or even entirely abolished The extensor muscles of the forearm are next in frequency to atrophy and as a

first, especially on the face later it undergoes a similar regression and the skin may be dry scaly, and wrinkled in the later stages of the disease The faces of these patients often present a senile appearance due to wrinkling and dryness

An early symptom of lepromatous leprosy is the alopecia of the outer half and later of the whole of the eyebrows The eyelashes may fall off as may the hair of the body especially in the axilla the pubis and the extremities The beard and mustache also become thinned out with finally a complete alopecia of the face The hair of the scalp is not affected in most cases but in others there may be patchy alopecia similar to and often indistinguishable from alopecia areata These patches often affect the edge of the scalp

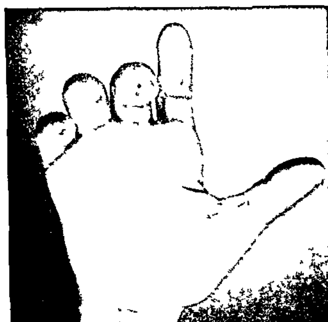


Fig. 11—Tuberculoid leprosy Leper claw Note ulceration of the finger tips and atrophy of the last phalanx

causing the *ophiasic* type of alopecia areata The alopecia of the scalp may be very extensive and the patient may be practically bald It is interesting to note that in the areas along the large blood vessels of the scalp the hairs are preserved the longest Although alopecia in leprosy has been considered as a dystrophic phenomenon it has been demonstrated by many including the author that the hair follicles in these cases of the lepromatous variety are surrounded by cellular infiltration very rich in acid fast bacilli

The nails in leprosy present many and varied dystrophic phenomena They are brittle discolored deformed twisted atrophic sometimes reduced to stumps on the ends of the atrophied fingers or toes The nails may be re

Leprosy of the ovaries and of the testicles is a frequent and an early occurrence in lepromatous patients which explains the sterility of the majority of patients with leprosy When these lesions develop early *in life they may* cause arrest of development these patients may have many of the characteristics of children or of eunuchs Lepromatous orchiepididymitis shows clinically by the presence of small lepromas of the size and shape of lead shot sometimes *larger* causing enlargements of the testicles lasting months or years with final atrophy and fibrosis Finally, the testicles are reduced to small nodules sometimes no bigger than olives These lesions may be among the earliest of leprosy present long before the skin manifestations become apparent in which case the differential diagnosis between the lesions of tuberculosis of the testicles and epididymis and leprosy may have to be considered

Enlargement of the breasts in men occurs rather frequently the mamma *being so prominent, due to the presence of lepromas and sometimes to true* hypertrophy of the glandular tissue that they become feminine in type Patients are very sensitive about this deformity and try to hide it as much as possible The relation of atrophy of the testicles to mammary hypertrophy has been pointed out

Nephritis is a common complication in the advanced periods of lepromatous patients the urine showing casts albumin and renal epithelial cells Hansen bacilli are often found in the urine being quite abundant in advanced cases Amyloid degeneration of the kidneys is a frequent autopsy finding Equally frequent in advanced and terminal cases are gastrointestinal cardiac and pulmonary complications

In lepromatous leprosy there is a bacillary septicemia the *Myco leprae* being easily demonstrated in the capillary blood as well as in the venous blood In tuberculoid forms such findings are never seen

In the great majority of patients with leprosy skin and neural symptoms are mixed in different proportions especially in lepromatous cases but skin and visceral symptoms predominate here with neural and dystrophic manifestations second in importance and frequency On the other hand in tuberculoid cases the skin symptoms are much less varied than in those of the lepromatous types while frequently the neural symptoms predominate visceral symptoms being usually absent The so called "pure neural leprosy" is a type of tuberculoid leprosy of the peripheral nerves with complete or almost complete absence of cutaneous *manifestations except for the atrophic* dystrophic and anesthetic symptoms due to the chronic degenerative neuritis The author has demonstrated that every case of this purely neural type belongs to the category of tuberculoid leprosy, the histologic changes constantly found in the nerves warranting this sweeping statement

In the simple inflammatory nonspecific type of leprosy, the lesions are first of the macular type on the skin and often also coincident with some neural enlargement and areas of anesthesia of the skin These cases are rare and are found only in the very early stages of the disease These are usually cases found when examining the contacts of leprosy cases and often as stated

result the hand effects several atrophic positions such as the so-called "monkey hand," "preacher's hand," and "ulnar claw," according to the degree of retraction of the several fingers and thumbs. Sometimes there are awkward and bizarre combinations of deformities of the hands and feet due to atrophy of the muscles, reabsorption of bone, and mutilations sometimes resembling those seen in chronic rheumatism. In the lower extremities similar deformities may be occasioned by atrophy of the muscles of the feet and calves and of the extensor muscles of the leg. The foot drop, similar to that seen in alcoholic and saturnine polyneuritis, is one of the most common phenomena of leprosy in the lower extremities. In the upper extremities hand drop due to radial paralysis is an infrequent phenomenon. The muscles of the face are paralyzed and later become atrophic due to polyneuritis of the facial and oculomotor nerves. The face becomes expressionless, indifferent, and occasionally there is a paralysis of the orbicularis oris with Bell's syndrome and a progressive atrophy of the muscles innervated by the facial nerve. All these muscular atrophies are more frequent and more extensive in cases of tuberculoid leprosy.

The bones of the extremities may suffer a process of reabsorption without ulceration so that the hands and feet seem shortened and deformed, so much so that the fingers and toes may be reduced to small stumps attached to the metacarpus with the atrophic residue of the nails on their ends. A frequent lesion, especially in the small bones of the fingers, is the so-called *analgesic whitlow* and also *Morvan's disease*. In these cases one or several fingers show inflammation and enlargement, quickly becoming necrotic and gangrenous with the elimination of sequestra, this process being entirely indolent.

VISCERAL LEPROSY

Lesions of leprosy in the viscera are almost exclusively limited to cases of the lepromatous type. Tuberculoid leprosy very rarely affects any of the internal organs.

The most frequently affected organs are the eyes, the anterior segment being the site of inflammation: conjunctivitis, iritis, keratitis, iridocyclitis and glaucoma. Chorioidoretinitis has also been observed. These inflammatory reactions very often end in complete loss of vision.

The lymphatic glands are frequently enlarged, one of the common symptoms of the lepromatous type, especially the glands of the groins and of the axillae. These glands are large, soft, with a certain amount of periadenitis and entirely painless.

Enlargement of the liver and spleen is a common symptom in advanced cases of the lepromatous type and jaundice may be observed in the final stages. The lesions are those of chronic hepatitis and cirrhosis. Autopsy reveals these organs studded with thousands of small lepromas very rich in Hansen bacilli and, in long-standing cases, with predominantly cirrhotic lesions and amyloid degeneration.

Loss of weight lack of the usual normal feeling loss of appetite and sudden increase in the rate of erythrocytic sedimentation are forerunners of a lepra reaction and should be an indication for rest in bed emptying the intestinal canal cessation of treatment with chaulmoogra oil or with Promin and the call to put the patient on a bland diet

LAZARINE LEPROSY

This rare variety of the disease was described first by Zambaco Pasha of Istambul (1897) and later by Pardo Castello and Caballero (1931) of Cuba and by Fernandez Vautrai (1941) of Brazil Leprologists are still undecided as to whether this is a distinct form of leprosy or whether it is simply a variety of the tuberculoid type Some leprologists ignore this type of the disease others consider that it consists only of the prevalence of the formation of bullae and areas of necrosis as a symptom of leprosy However the cases seen by the author and Guillermo Caballero in Matanzas Cuba were to all appearances genuine cases of *monosymptomatic leprosy* consisting of the development of areas of necrosis at the site of an edematous infiltration or of a bloody bulla in a formerly apparently normal person These lesions progress with destruction of the subcutaneous tissue the tendons and muscles and even to the extent of opening of the joints of the extremities causing tremendous mutilations The progress is slow and healing of these necrotic areas leaves retracted and atrophic scars These lesions are always indolent frightful mutilations apparently with no pain whatsoever The diagnosis is made by bacteriologic examination of the necrotic tissues where millions of acid fast bacilli are found with all the characteristics of the *Myco leprae* All attempts to cultivate these bacilli have ended in failure The pathologic anatomy of the affected tissues is that of a tuberculoid infiltration ending in necrosis which is a phenomenon never seen in the usual types of tuberculoid leprosy It is easy to find acid fast bacilli in enormous numbers in the bullae which are the first lesions to appear

The outcome of these cases is occasionally fatal More often the ulcers heal leaving deformities and anesthetic scars and the patient may recover or suffer later from the chronic lesions of leprosy

THE DIFFERENTIAL DIAGNOSIS OF LEPROSY

The diagnosis of leprosy offers no difficulty in the great majority of cases especially the lepromatous type The coincident cutaneous and neural lesions disturbances of sensation and the dystrophic manifestations are characteristic However in some types of leucemia cutis affecting the face the cutaneous nodules and infiltrations "en nappe may simulate the *leonine facies* of leprosy In these cases the absence of anesthesia to pain and temperature as well as the histopathologic changes and the absence of acid fast bacilli will settle the differential diagnosis Mycosis fungoides may offer a similar problem in some cases

above, the patients are unaware of the presence of such lesions It must be emphasized that these patients sooner or later become either lepromatous or tuberculoid cases and this possibility may be predicted by the result of the lepromin test (see p 589)

LEPRA REACTION

Leprosy is a chronic disease lasting many years presenting varied and progressive symptoms over a period of months and years During this chronic course, however, acute episodes may occur these are known as *reactions* or better as *lepra reactions* Occasionally leprosy is initiated with one of these acute attacks the first intimation that the patient has any pathologic condition

This acute condition is characterized, in the lepromatous cases by malaise headache backache chills fever, peripheral painful neuritis, and outbreaks of new nodular lesions bright red in color which may develop in a few hours and which resemble an acute attack of erythema multiforme The fever may be as low as 37.5° C or as high as 41° C with morning remissions and even exacerbations The peripheral neuritis may be accompanied by excruciating pain making sleep impossible The rash composed of erythematous patches papules nodules and urticarial plaques may invade the whole skin surface and the patient seems swollen and deformed beyond belief Old lesions may show central necrosis and ulceration In some patients enlargement of the liver and spleen and acute orchiepididymitis have been observed The patient may die in this acute condition, however that is a rare occurrence As a rule the condition lasts a week or a few months and gradually subsides At times patients remain in acute attacks with very little remission for 6 months to a year

Needless to say, the occurrence of repeated acute attacks aggravates the prognosis in leprosy

During the attacks of lepra reaction the bacilli may be found in huge numbers in the tissues in the peripheral blood in the venous blood and even in the arterial blood Erythrocytic sedimentation rate may be very rapid usually 100 mm or more during the first hour

In tuberculoid leprosy lepra reaction develops in a less dramatic fashion Fever is usually absent and if present is rarely above 38° C There may be activation of the pre existing lesions and a few others may appear Peripheral neuritic pains may be quite troublesome and bacilli may be found in scant numbers in the swollen lesions The patient is usually able to go about and do his chores without much trouble contrary to lepromatous patients in lepra reaction *These must remain in bed unable to move for weeks and months* during which time they may become emaciated and progressively weaker In the acute phase of tuberculoid leprosy the erythrocyte sedimentation rate is seldom much increased usually not more than 20 mm during the first hour

Lepra reaction may be brought about by injudicious treatment with Promin or chaulmoogra oil by intercurrent diseases by excessive eating or drinking by excessive exercise by sexual debauches or at times it may occur without any apparent reason

Loss of weight lack of the usual normal feeling loss of appetite and sudden increase in the rate of erythrocytic sedimentation are forerunners of a lepra reaction and should be an indication for rest in bed emptying the intestinal canal cessation of treatment with chaulmoogra oil or with Promin and the call to put the patient on a bland diet

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The tuberculoid types of leprosy of the skin and of the nerves may cause difficulties in diagnosis more often than the lepromatous types. Here the cutaneous lesions may be difficult to differentiate from those of sarcoidosis, so much so that some investigators believe that sarcoidosis may be due to *Myco. leprae* in some cases. However, the diagnosis may be made by the histamine test and by the presence of anesthesia in leprosy and its absence in sarcoidosis, but the clinical picture as well as the histopathologic findings may be very similar. *In cases of the pure neural tuberculoid syndrome of leprosy* confusion with syringomyelia is quite possible, but the usual enlargement of the ulnar nerves and the histamine test which remains normal in syringomyelia are sufficient to establish the diagnosis. Alcoholic and diabetic polyneuritis, as well as the polyneuritic syndrome due to avitaminosis, beriberi, lead and bismuth may cause confusion, but they are not difficult to differentiate. In any case biopsy of the ulnar nerve will settle the diagnosis of leprosy.

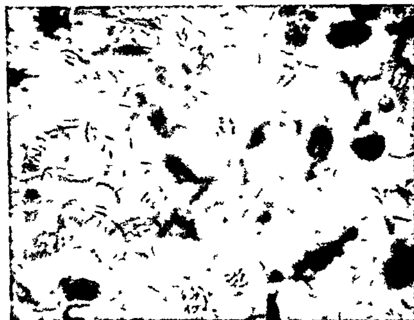


Fig. 178.—Section of lepromatous case. Note the clear spaces (globi) filled with bacilli.

The acute attacks of lepra reaction may be mistaken for acute erythema multiforme, allergic reactions to drugs or food, erythema nodosum of streptococcal nature, and the exanthematic fevers. In countries where leprosy is endemic a diagnosis of acute leprosy must always be in the mind of the general practitioner, and in these cases the presence of Hansen bacilli is usually easy to demonstrate.

It must be emphasized here that the presence of Myco. leprae in the nasal secretions, in the capillary blood, or in dermal scrapings is diagnostic of leprosy.



Fig 1.4 —Section of tuberculoid leprosy of the skin Typical sausage shaped infiltration resembling sarcoid

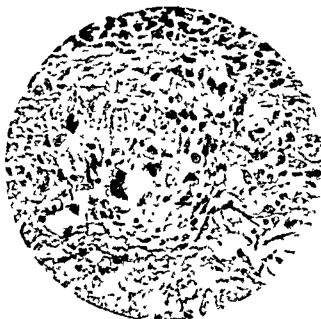


Fig 175 —Section of ulnar nerve showing typical tuberculoid structure in a case of tuberculoid leprosy limited exclusively to the peripheral nerves (formerly called neural leprosy)

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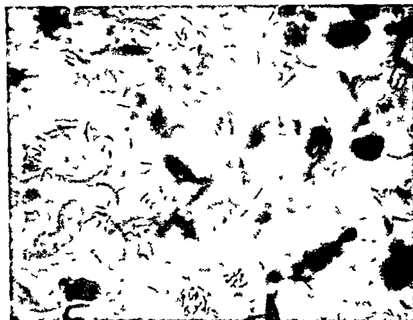


Fig 173 —Section of lepromatous tissue Note the clear spaces (globi) filled with bacilli

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Similar tests made with salt *solution and with distilled water cause a fleet* reaction similar to the one described above However these reactions are r constant and may be more or less absent or more or less marked according the personal reactivity of the patient due to the individual capacity to libera ' H substance under the trauma of the needle point

This test is adequate for the diagnosis of areas of anesthesia or of ear erythematous lesions due to leprosy especially in children and in noncooperati patients

It must be pointed out however that any type of degenerative peripher neuritis may give an abnormal histamine test and that therefore it is n *exclusively diagnostic of leprosy Furthermore the test is not reliable wh* performed at a room temperature below 24° C or when performed on ag persons with slow or impaired peripheral circulation

It is important in the differential diagnosis between leprosy and syring myelia since in the latter condition the histamine test is normal

The test is read as *normal* or *abnormal,* not as positive or negative

PROGNOSIS OF LEPROSY

The outlook for a patient with leprosy (untreated) is usually unfavorabl Leprosy is a chronic progressive disease especially the lepromatous type The prognosis is therefore grave and only when the cases are recognized an diagnosed early in the disease can one be optimistic as to the future How ever patients with the tuberculoid type of the disease often suffer only fro a few dyschromic or erythematonodular lesions without any discomfort livin a happy and useful life These tuberculoid types have been known to regre and remain asymptomatic for the remainder of their lives which amoun to a spontaneous cure Even in moderately advanced cases of tuberculoi leprosy with enlargement of the ulnar and other nerves and atrophy and r traction of the hands the disease may remain arrested after a number of yea and no further symptoms appear In lepromatous leprosy occasional patient heal after a time usually years the patient presenting no apparent new symp toms but remaining maimed wrinkled senile like with distorted extremitie and *deformed nose* These have been called the 'burned out lepers' and *such cases Myco leprae may be absent*

These remarks refer to cases left without any attempt at treatmen When the patients are properly housed fed and treated the prognosis ma be better and a certain number of cases of leprosy get well although carryin forever the scars of the disease The number of patients paroled from lepro saria as arrested or probably cured is increasing and newer methods o approach to treatment and hygienic measures promise a still greater propor tion of discharges

Most patients of the lepromatous type of leprosy progress toward dis ability blindness laryngitis with occlusive inflammatory lesions leading t tracheotomy cachexia and death Some patients are the victims of inter current disease but it is to be noted that tuberculosis is not frequent amon these patients

but absence of the organism does not exclude the possibility of the existence of this disease It must be remembered that it may be impossible to demonstrate *Myco lep rae* in the macular lesions of the simple inflammatory type and in the tuberculoid lesions of the skin and nerves

The diagnosis of the early macular lesions or of the areas of anesthesia without morphologic skin changes so often found in contacts when following up leprosy patients may offer a serious diagnostic problem and at times the definite diagnosis must be postponed for lack of evidence In these cases the histamine test may be the only method of diagnosis

The Histamine Test

Among the pharmacodynamic tests used for the study of circulatory physiologic and peripheral innervation the histamine test is the most important for the dermatologist It is of very great importance in the diagnosis of leprosy syringomyelia polyneuritis and areas of anesthesia of central and peripheral origin

Technic —

Place a drop of 1 1 000 solution of histamine phosphate on the affected skin to be tested.

Place another drop at a point between the suspected area and the adjacent normal skin and a third drop on the normal skin

Lightly prick the epidermis through these drops using the point of a hypodermic needle being careful not to cause bleeding

Immediately dry the drops of histamine with cotton and carefully watch the sites of the test

Within 25 to 40 seconds after the pricking of the skin the *normal skin* shows an area of erythema with irregular outline usually 5 to 20 mm in diameter later reaching as much as 5 centimeters

In 60 to 100 seconds a wheal forms in the erythematous area centered by the point where the needle entered the epidermis Finally after 3 minutes a hemorrhagic point may appear at the site of the needle prick The wheal usually measures 2 to 5 mm in diameter

The reaction persists for approximately 20 minutes but at times the erythema and the wheal are still present after 45 minutes There are individual variations due to age room temperature and local circulatory conditions The test is useless on the Negro skin

The test on the place *between the affected and the normal skin* shows the same succession of phenomena on the normal half of the skin but on the affected half the erythematous reaction stops abruptly and is absent on that part of the skin but the wheal is always present without the peripheral erythema

On the *anesthetic skin* erythema is wholly lacking while the wheal is present and remains the usual length of time

The test causes no subjective sensations either on the normal or on the affected skin

The test has also been made by scarification and by intradermal injection of histamine but results are more clear cut with the technic described above

at home under sanitary supervision and under the proper treatment There is no more reason to segregate these patients than to segregate early cases of pulmonary tuberculosis when no bacilli are found in the sputum

Leprosy is not a highly contagious disease, and the fear that its presence causes in a community is unjustified It is accepted by all leprologists that contagion of leprosy requires prolonged contact with a patient of the lepromatous type, defective hygienic surroundings, and poor bodily defenses Attendants nurses, employees, doctors, Sisters of Charity and of other religious orders caring for these patients remain healthy and unaffected after years of contact with leprosy patients, and they use only the logical preventive measures that any other bacterial disease requires

The treatment of the disease itself calls, in the first place, for a complete examination of the patient to set aright any deviation from the normal health that may be found, such as intestinal parasites disturbances of gastric or intestinal digestion liver disorders, focal infections, parasitic skin diseases anemia malaria, avitaminosis, and others The patient must be placed in the best possible physical condition to resist the spread of the disease of leprosy The importance of hygienic and nutritional measures cannot be overemphasized here and in this connection leprosy shows as marvelous an improvement as tuberculosis under the proper combination of rest or exercise as the case may be nutritious food high in caloric value and in vitamin content, clean living quarters and plenty of fresh air and sunshine

Milk in plentiful amounts, fresh meat, fish, and poultry, simply cooked and condimented, vegetables, fruits, sugar in plentiful amounts starches in the form of cereals potatoes and other tubers supplemented by calcium salts and vitamins, form the menu of patients with leprosy Eggs may be eaten in moderation, fats in small amounts, but as a rule butter and lard as well as oils should be used sparingly Pork sausages, salted meat, fish, and fried foods are entirely forbidden Chocolate, cakes and pastries are allowed on few occasions, and alcoholic beverages are prohibited Desserts should consist of stewed or preserved fruits, gelatin, hard candies, Junket, and other milk desserts

There is no specific treatment for leprosy Two methods of treatment are used at present with fair percentage of success when treatment is started early in the disease chaulmoogra oil and certain sulfonated drugs, of which Promin is the best known

Chaulmoogra oil is obtained by the expression of seeds of several trees of the *Hydnocarpus*, *Teraktogenos*, *and also in Brazil of the Carpotroche* families The best known species are the *Hydnocarpus wightiana* and the *Teraktogenos kurzii* The expressed oil must be refined neutralized and sterilized before use The ethylic and benzylic esters of chaulmoogra oil have also been used

In the experience of the author and his associates, the best preparation is the refined and neutralized chaulmoogra oil in the form of intradermal and intramuscular injections The ethyl esters are painful and often cause

TREATMENT*

Treatment must be considered first from the point of view of prophylaxis and second from the point of view of treatment of the individual

The most important prophylactic treatment concerns isolation of the patients in sanitaria hospitals or colonies The present tendency among the foremost Brazilian and Argentinian leprologists is to segregate these patients in colonies that is in small communities of about 500 to 1 000 people, with homes stores clubs theaters sports fields and hospitals and dispensaries Here these patients living as they would at home can visit their doctors in the dispensaries to receive advice and treatment as often as needed while performing their work in the community and contributing to their own support These colonies produce their own dairy products truck gardens meat and other products while the inmates help to keep the community clean and orderly being properly remunerated for their work

When a wage earner is committed to one of these colonies his family is cared for by the authorities and properly protected there being for the children institutions called *preventoria* where they are educated and taught a trade until the age of 18 when they are discharged equipped with the necessary instruments or tools for their work

Each institution is equipped with hospital facilities for intercurrent diseases and with beds for chronic disabled patients

One of the most important measures for the prophylaxis and early detection of cases of leprosy is the careful and minute examination of those who have been in contact with a leprosy patient—the near relatives the friends and the neighbors of such patients These contacts frequently have a few undetected symptoms of early leprosy and offer the best opportunity for quick and successful treatment The author has found a number of such cases with one or two isolated lesions where surgical removal of such lesions has been successful and these patients have remained without further symptoms of the disease This fact leads to the belief that leprosy may be locally inoculated into the skin and remain as a localized condition for some time

The treatment of leprosy requires devotion and faith on the part of the physician as well as of the patient The mental attitude of these patients especially when fugitives from sanitary authorities or when finally segregated must be taken into consideration That is why the type of institution recommended and used by the South American leprologists is the most humane and effective of all the patients may live as normal human beings do their work have their homes and in cases where a whole family is affected live as a unit The will to live the hope of getting well and a busy life are important factors contributed by the patient in the treatment of leprosy

It must be stated here that it is not necessary to segregate patients with the simple inflammatory or the tuberculoid type of leprosy unless they cannot live within the set of rules advised by the sanitary authorities or when they are destitute In cases of tuberculoid leprosy or of the early simple inflammatory type with no Hansen bacilli are demonstrable these patients may remain

*See also Chapters 64 and 65

The oral administration of chaulmoogra oil has been abandoned because of the gastric and intestinal disturbances which it causes which prevent the use of therapeutically active doses Intravenous injection of the oil has also been recommended, but it causes acute discomfort, coughing attacks, dyspnea cephalic congestion, tachycardia, and other untoward symptoms It is not advised

Chaulmoogra oil may be used for long periods of time in the manner described above The degree of improvement varies with different subjects It is practically nil in some cases *The steady improvement of others makes* this method of treatment an excellent therapeutic procedure which should be tried in every case In cases of tuberculoid, early simple inflammatory lesions, and early cases of lepromatous types, the success of chaulmoogra oil is at times slightly less than miraculous

It must be stated here that successful treatment with chaulmoogra oil requires a strong and healthy patient, and that the general hygienic measures *already explained the use of calcium, vitamin B complex, and plenty of fresh* air, graduated exercise and rest, proper living habits, and wholesome food are a sine qua non for success Anemic, undernourished patients and patients with intestinal parasites, improper feeding habits, and low defenses do not tolerate chaulmoogra well and their condition becomes aggravated under this treatment

Promin (Parke, Davis & Co), the sodium salt of *p,p'* diamino diphenyl sulfone N N' di(dextrose sodium sulfonate), used originally in the therapeusis of tuberculosis, was used for the first time by Faget and his associates of Carville La in the treatment of leprosy in 1943 (1943 1945) with encouraging results Promin was later considered by Faget and his associates as the best drug ever used in the treatment of leprosy The author and his associates (1946) in 1945 and 1946 used Promin in the treatment of over 30 cases of leprosy with promising results and remarkable improvement in some cases

Promin is furnished in capsules containing 0 20 Gm and 0 40 Gm each for oral use, and in ampules containing 1 Gm of the product in 2 c c of water for intravenous use Promin causes hemolytic anemia and therefore must be used with caution The dosage by mouth varies from 0 20 to 1 20 Gm per diem, and intravenously from 1 to 5 Gm per diem, usually 6 days a week, resting on Sundays The intravenous injections are much better tolerated than the orally administered capsules, and, therefore, at present only the intravenous route is used Treatment is continued for several months with an *occasional* 2 weeks of rest In the author's experience, one patient was able to tolerate a year of continuous treatment with oral Promin, with steady improvement and without any untoward symptoms Anemia is treated with iron salts and good food, but occasionally treatment with Promin must be discontinued due to the low hemoglobin and erythrocyte count Intestinal disturbances, icterus neuritis dermatitis exfoliativa, eczematous reactions and a bluish discoloration of the skin are often observed but *seldom require discontinuation of* the treatment with Promin Lowering the dose, or at the most providing a few weeks rest,

muscular infiltrations and nodular formations The benzylic esters are less irritating to the muscles but offer no special advantage over the pure refined oil

Chaulmoogra oil as received in tin containers from India and Burma is mixed with dead leaves pieces of bark and other detritus and has an acidity of 2 to 3 per cent due to the presence of fatty acids This oil is mixed with petroleum ether in the proportion of approximately 1 part of oil to 15 parts of petroleum ether This solution of the oil is treated with an amount of 38 per cent sodium hydroxide equal to the acidity of the oil The potassium salts of the fatty acids thus formed are separated in the form of soaps To this turbid solution anhydrous sodium sulfate is added the whole filtered and distilled evaporating the residue in vacuum The resulting oil practically neutral in reaction lighter than the original oil is distributed in ampules and sterilized The best chaulmoogra oil deviates polarized light to the right an average of 48°

This oil is injected intramuscularly in doses varying from 1 to 10 c c into the gluteal muscles These injections are at first given once a week later 2 or 3 times a week with a total dosage of 5 to 30 c c weekly As a rule the tolerated dose is about 15 to 20 c c weekly although some exceptional cases may be able to tolerate as much as 30 and 40 c c In most cases 5 c c 3 times a week is well tolerated The dosage must be used according to the weight and the tolerance of the patient Women as a rule are unable to tolerate as high doses as men and in children the dose of 3 c c twice a week is a fair amount In the experience of the author extremely high doses are unnecessary and the maximum of 20 c c weekly for adults is advised It is wise to start treatment with 1 c c twice a week increasing gradually Painful reactions fever increase in the sedimentation rate loss of weight loss of appetite are signs of intolerance in which case treatment with chaulmoogra oil should be stopped and later begun in smaller and slowly advancing doses Continuance of treatment in the presence of the symptoms mentioned above exposes the patient to the danger of an acute lepra reaction After the patient has received 300 c c of the oil it is advisable to allow a rest period of at least 1 month

In early cases and in the macular and tuberculoid lesions the intradermal use of chaulmoogra oil is of great benefit The oil is injected into the dermis of the affected skin in doses of 0 1 to 0 2 c c with a fine needle A certain amount of the oil always flows back along the path of the needle but the wheal caused at the site of the injection insures local absorption of the greater part of the oil dermally injected In this manner the local lesions receive from 1 to 3 c c of the oil and the rest of the dose is injected intramuscularly The advantage of this method of treatment is apparent in the more frequent and quicker resolution of the local lesions which often disappear in a few months leaving only areas of anesthesia which are usually permanent The author strongly recommends the intradermal use of chaulmoogra oil especially in the tuberculoid lesions of leprosy

in cases of chronic painful neuritis, tracheotomy, and amputation of certain fingers and toes when beyond hope of repair

Penicillin and other antibiotics have no effect on leprosy, but they are very useful in the treatment of secondary infections, in the clearing up of chronic ulcers and infections of the eye, ear, nose, and throat

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allows the resumption of the optimum amount of Promin by the intravenous route The maximum dose of 5 Gm is not well tolerated and it is better not to go above 3 Gm for women and 4 Gm for men

Promin is not a specific for leprosy It does not seem to act bacteriolytically against *Myco leprae* since, even after prolonged treatment, numerous bacilli are seen in the slowly receding lesions Its therapeutic action is more marked on the lesions of the mucous membranes, and a rapid improvement in the rhinitis, laryngitis, and mouth lesions are usually among the first favorable results The cutaneous lesions improve more slowly and gradually, and some are not affected, while in some cases new lesions appear even while the patient is under treatment with Promin The eye lesions also show remarkable improvement The thickened nerves do not show any improvement under treatment with Promin

Promin is a valuable addition to the treatment of leprosy but must be used with caution, and no definite results can be predicted

Promizole, a later improvement on Promin, has been used recently by physicians of the Carville Leprosarium with favorable results

Treatment of the acute lepra reaction is one of the most important and difficult problems Chaulmoogra oil is entirely contraindicated in these cases, and Promin does not seem to have any action on the symptoms of this unpleasant and serious complication The careful watch on the sedimentation rate, the temperature, and the weight of the patient may warn the attending physician of the impending acute reaction, and by stopping chaulmoogra treatment in time, he may be able to prevent its occurrence *

Patients with acute lepra reaction must be put to bed, a saline purgative administered, and a light bland diet prescribed All previous medical treatments must be stopped Calcium gluconate, hypertonic dextrose solution, and **antimony and potassium tartrate,** 1 per cent solution in 1 to 5 c c doses intravenously, are the best therapeutic measures The intravenous administration of antimonium and potassium tartrate is the treatment of choice, and in some cases it is the only measure that will control the temperature and make the patient comfortable Treatment may be continued for days and weeks without any apparent disturbance except an occasional backache or arthritic pain Very often the lesions of leprosy retrogress under the use of this antimonium salt, the patient regains his normal weight, and the sedimentation rate returns to normal The author has used treatment with this antimonium salt in cases of this sort for months, with very beneficial results for the patient

Other procedures that may be of benefit in certain cases of leprosy are large doses of thiamin chloride, 100 to 200 mg daily, cauterization of ulcerations and lepromas of the mucous membranes with trichloracetic acid, removal of troublesome lepromas, neurotomy, or dissociation of the nerve trunk

*Editor's note (O F) Johansen and Erickson (Proc 4th Internat. Congr Trop Med and Malaria 1948) emphasize that correction of deformities and disfigurement, by plastic surgery are successful in Promin Diasone, and Promizole treated patients.

peruana and Oroya fever were manifestations of the same disease (in Odriozola, 1898) Among other cases, Espinal refers to that of an American engineer who suffered from Oroya fever in Peru, and later, after his return to the United States, had an eruption of verrugas

In 1885, Daniel A Carrion, a medical student, inoculated himself with verruga material After 21 days of incubation, he developed a disease with the typical symptoms of a clinical attack of Oroya fever Carrión himself diagnosed it as such The disease progressed to a fatal end after 18 days of illness According to La Puente, Loli, and Vega pallor of the skin was noted at autopsy, the liver was enlarged, the mesenteric lymph nodes were hypertrophied, almost doubled in size, while the spleen was not as heavy as usual (in Weinman, 1944) It is clear that after an inoculation of verruga material, Carrion developed a typical clinical attack of Oroya fever Hence the conclusion followed that Carrion had demonstrated the etiologic identity of the epidemic disease, Oroya fever with the old known verruga In his memory, the name of "Carrión's disease" was given to the malady

In 1898, Odriozola's monograph "La maladie de Carrion ou la verruga peruvienne" appeared It is an excellent work in which all the data known up to that time were carefully summarized In 1905 Barton discovered the etiologic agent of the disease, *Bartonella bacilliformis* (Strong et al, 1915), in the red blood cells of patients with Oroya fever In 1913 the Harvard Commission, Strong, Tyzzer, Brues Sellards, and Gastiaburu made original and valuable investigations on certain aspects of the disease This commission reached the conclusion that Oroya fever and verruga peruana were two different diseases Although the common opinion of Peruvian scientists was that the two syndromes were of the same origin (based on clinical, epidemiologic, and experimental findings), at that time absolute and complete proof of the etiologic unity was still lacking It was not until 1926 when Noguchi and Battistini published their methods for the cultivation of *B bacilliformis* that it was shown that cultures from verruga and Oroya fever patients contained the same microorganism These microorganisms behaved consistently in the same manner in cultures as when injected into monkeys The identity of the two diseases was proved, beyond any doubt, by these studies The Harvard expedition to Peru in 1937 fully confirmed this theory

Space prevents review in detail of all works performed by Peruvian investigators. The contribution of Peruvian medicine to the knowledge of Carrion's disease is really outstanding

Our knowledge of human bartonellosis has increased substantially in recent years but there are still many important questions unsolved In 1944, Weinman published his excellent monograph *Infectious Anemias Due to Bartonella and Related Red Cell Parasites*, in which not only the actual data on bartonellosis are fully presented and discussed, but the unsolved problems in this field are carefully defined The reader is referred to this monograph for further information

ETIOLOGY

Morphology

The etiologic agent of Carrion's disease, *Bartonella bacilliformis*, presents an extreme *degree of pleomorphism Coccus like, ring, oval, rod shaped (straight, or* more or less curved), and granular forms are found The arrangement of the microorganisms in the red blood cells is also variable Sometimes they form a short chain of cocci or a chain of rods, or they may resemble Chinese letters or a circumflex accent The size of the coccus like forms is 0 3 to 1 micron, and that of the rods 0 5 to 3 microns Curved rods of 7 microns have been seen, but not frequently *B bacilliformis* is gram negative and is stained reddish violet with Romanowsky stains, such as Giemsa Frequently bipolar staining is observed

CHAPTER 32

HUMAN BARTONELLOSIS OR CARRIÓN'S DISEASE

HERNANDO GROOT

DEFINITION

Human bartonellosis or Carrion's disease is a pathologic condition produced by *Bartonella bacilliformis*. It is characterized by a first period in which the pathogenic microorganism may be found in large numbers in the peripheral blood accompanied by a variable degree of anemia and usually pains and fever. The symptoms may be very severe or on the contrary absent and between these extremes cases showing intermediate phases of symptomatology may be found. After this period in most cases a second stage follows in which appears an eruption of small hemangioma like tumors with or without deep nodular elements. The eruptive element has been designated with the name verruga and is known in the medical literature as verruga peruana. The names Oroya fever and less frequently Carrion's fever have been given to the severe forms of the first period in which the final outcome is frequently death. For a better understanding in the present discussion the two periods of the disease will be designated as the noneruptive stage and the eruptive stage respectively.

HISTORICAL REVIEW

It is quite probable that bartonellosis existed in Peru before the discovery of America. Reproduction of the verrugas have been found in statuettes and pottery made by the pre Colombian Indians in Peru who as it is well known possessed a high degree of culture and medical knowledge (d'Harcourt 1939). During the Spanish Conquest in 1531 Pizarro's soldiers were attacked in Coaque Ecuador by a severe unfamiliar disease (Pizarro 1571) which has been considered as bartonellosis. The chronicles of that time designated the disease as Verrugas. Although Maldonado (1931) who has carefully studied historical data thinks that this epidemic was a combination of yaws and malaria it is generally believed that the disease observed in Coaque was bartonellosis. It must be mentioned however that verrugas has not been reported from this region in recent times. The first medical document on the subject by the Peruvian physician Gago de Vadillo was not written until 1630. In the subsequent years there appeared several references to the eruptive stage of the disease among them one of Bueno and later those of Unanue (in Rebagliati 1940) are remarkable. But it was not until the nineteenth and twentieth centuries that really significant knowledge of the malady was gained.

In 1870 a severe disease of obscure origin characterized by fever and anemia attacked the workmen of the Central Railway in the region between Lima and Oroya particularly in the zone between the towns of Chosica and Maturana. It appeared in epidemic form and caused a large number of deaths (approximately 7,000). The Peruvian physicians became greatly interested in the epidemic and the name Oroya fever was given to the disease. Different opinions were held in regard to the origin of such an epidemic. Among them it is important to note was that of Espinal who thought verruga

Motility

In fresh preparations of blood from Oroya fever cases, it is possible to recognize a very slow movement of the Bartonellae within the infected red cells. In young cultures *B. bacilliformis* is motile. Special flagellar stains such as Zettnow reveal three to five unipolar flagella (Geiman, 1944). Using dark field illumination, nonmotile spirals are frequently seen in cultures. These spirals are sometimes quite long, up to 50 microns. They have been considered as abnormal cast off flagella. Such spirals have not been seen in dark field preparations of fresh blood from Oroya fever patients.

Cultivation*

B. bacilliformis does not grow in ordinary media. *Blood agar and Noguchi semisolid* medium for leptospira have been commonly employed. In Noguchi's medium, growth becomes grossly visible near the surface of the medium in about 5 to 15 days. This growth appears often as a nebulous zone 5 to 10 mm. below the surface of the medium. Sometimes, especially in cultures from blood, more or less isolated, granular colonies are observed. It is not rare *that in this medium the growth is poor or, if obtained, is realized with considerable difficulty.*

More recently several media have been developed. Pinkerton and Weinman (1937a) have shown that in tissue cultures *B. bacilliformis* develops within the cytoplasm of cells as well as in the surrounding medium. Jimenez (1940) has used successfully beef infusion agar to which cystine, glucose, and rabbit blood were added. He has also shown that the *x* factor is necessary, but not the *v*, for the growth of Bartonella. Jimenez and Buddingh (1940) have cultivated the organism in the chorioallantoic fluid of the developing chick embryo, 8- and 12-day old embryos were used, and the incubation was performed at 25° to 28° C. Chorioallantoic fluid, aspirated by a pipette and transferred to test tubes, also proved to be successful.

The best results are obtained by using the media devised by Geiman (1941).*

Classification

The general consensus is to classify *Bartonella bacilliformis* as a bacterium. Topley and Wilson (1945) place this microorganism among "miscellaneous bacteria." *We do not* know yet, with certainty, where among the bacteria it should be placed. The genus Bartonella was created in 1913 by Strong et al.

Repeatedly marked resemblances of human Bartonellae to Rickettsiae have been pointed out, and Strong (1942) believes it is wise to separate both from the true bacteria and from the filtrable viruses. *Alzamora* (1945) *believes Bartonella should be placed in an intermediate position between true bacteria and Rickettsiae.*

EPIDEMIOLOGY

Geographic Distribution

The disease is known to occur only in certain regions in western South America. The zone extends from approximately 2 degrees north to 13 degrees south latitude. In Peru, the disease is observed in two regions: one, the Pacific watershed, which includes 21 zones and corresponds to equal numbers of hydrographic formations that extend from the western *slopes of the Andes to the Pacific, the other*, the Marañon watershed formed by the regions around eighteen rivers in the Amazon basin (Rebagliati, 1940). In Ecuador the disease has been found in the provinces of El Oro (Hertig, 1940), and Loja (Montalvan, 1940), near the Peruvian border. In Colombia, bartonellosis occurs in the southwest of the country, in a large area around the city of Pasto (Patiño Camargo, 1939).

*See Chapters 71 and 73.

In the endothelial cells lining blood and lymph channels of viscera from fatal cases of Oroya fever, the organisms are sometimes discrete and rod shaped, but most commonly they appear as granular or amorphous round masses, which distend the cells Sometimes in the edges of these clusters, organisms with more or less typical morphology are seen

In the cutaneous nodules *B bacilliformis* appears within the endothelial cells as rod shaped organisms or as clusters of microorganisms However, the size of such clusters is not as large as that usually observed in the visceral cells from cases of Oroya fever



Fig 176—*Bartonella bacilliformis* in the peripheral blood from a case of Oroya fever Giemsa stain (×1480) (Photograph by C Sanmartin.)

Pinkerton and Weinman (1937) have shown that *B bacilliformis* grown in tissue cultures, appears early as small spherical clusters, 3 to 10 microns in diameter, of sharply stained diplobacillary rods in the cells Later usually by the sixth day the cells are packed with clusters of less discrete organisms, often coccoid, granular, or amorphous in such a way that they give a picture quite similar to that observed in infected endothelial cells from cases of Oroya fever

In other media,* such as Noguchi s leptospira medium or Geiman semisolid or solid medium, the different forms of the Bartonellae are seen, but commonly they appear as clusters of organisms in which it is not easy to recognize the individuality of the parasites except in the periphery Sometimes in these clusters, when Giemsa stain is used, it appears as if the organisms were embedded in an amorphous substance stained a lighter blue The author has observed that in order to study the morphology of the Bartonellae in such cultures it is sometimes advantageous to stain with diluted fuchsin

*See Chapters 71 and 73

of *B bacilliformis* from the intestines of females of *P verrucarum*, which had fed about 60 hours previously (1942) The same author obtained pure cultures of *B bacilliformis* from wild sand flies He has found also that frequently the three species of Peruvian Phlebotomi in the endemic area may present massive infections of the tip of the proboscis with an unnamed organism in certain aspects similar to *B bacilliformis* Such infections have been found in males and in females, and in females which have never had a blood meal

*Phlebotomus belongs to the family Psychodidae of the order Diptera *Phlebotomi* are small, moth like flies, rarely exceeding 5 mm in length Their bodies and wings are densely covered by hairs They may be distinguished easily from other Diptera by the position of the wings which are held upward so that the costal margins form angles of about 60 degrees with each other and with the body (Hertig, 1942) Only the females are hematophagous Their flight is noiseless and oscillating when disturbed During the day they hide on walls in dark corners in dark rooms, caves, crevices, etc The breeding places are difficult to find These are moist, dark places, with organic matter, under stone, in rock interstices in cracks of old walls, in chicken houses In the endemic areas in Colombia, Phlebotomi are found in enormous numbers in the humid and dark caves where Panama hat weavers work

Hertig states that *P verrucarum* readily bites man, enters houses freely, and is found associated with man and domestic animals, both in buildings and in outdoor places far from human dwellings *P peruensis*, similar in habits is scarce when compared with *P verrucarum* *P peruensis* is usually found in the upper limit of the verruga zone *P noguchii* appears to have an entirely outdoor existence, and does not bite man This sand fly commonly feeds on field mice

Probably in Colombia as in Peru, the insect vector is a Phlebotomus Several species of Phlebotomi have been found in the Colombian endemic areas but not those usually found in Peru The recorded Colombian species are *P longipalpis*, *P evansi*, *P osornoi*, *P colombianus*, and *P monticolus* var *incarum* (Ristorcelli and Dao, 1941)

Sources of Infection

The only known reservoir of virus in human bartonellosis is man Man and the insect vector are the only living beings known to be naturally infected with *B bacilliformis* Man may have the microorganism in the peripheral blood long before the appearance of symptoms during the different manifestations of the disease, and for a long time after the clinical attack The existence of asymptomatic human infections in people living in endemic zones, either with or without previous history of the disease, has been demonstrated several times (Battistini, 1927, Mackehenie 1934, Weinman and Pinkerton, 1937, Howe, 1943a, Groot, 1946) The incidence of such carriers in the infected areas is significantly high—10 per cent—perhaps higher Thus, from the present data, the importance of man as a source of infection appears to be clear

In these three countries the disease is observed in the same system of mountains, the Andes, in regions with similar definite conditions of topography, hydrology, climate, fauna, and flora These zones are found in the narrow valleys formed by rivers and streams between mountains, and in the highly inclined slopes of these, near the water courses The climate is relatively hot in the day and cool during the night In Peru the vegetation is rather luxuriant down in the valleys, but scanty in the surrounding mountains The zone is sparsely inhabited In that country the disease is endemic at altitudes between 500 and 3,000 meters (1 640 and 9 840 feet) above sea level The lowest verruga zone recorded by Rebaglati (1940) is Esquina de Asia, at 200 meters (656 feet), but it is not stated that these cases were not imported (Weinman, 1944) The highest zone, according to the same author, is Huasta, at 3,375 meters (11,700 feet) In Colombia, according to the present available information, bartonellosis exists only at places with altitudes between 1,300 and 1,850 meters (4,260 and 6,000 feet), with daily temperatures of 18° to 25° C (64° to 77° F), somewhat lower during the night, and with the same conditions as previously stated, except that these regions are densely populated and that the soil is very fertile and the vegetation abundant in the slopes of the mountains as well as in the valley bottoms In Colombia the upper and lower limits of the zone are sharply defined In many places in which the density of houses and population is the same above and below 1,850 meters (6,000 feet), all persons who live above such altitude have nevertheless remained free from the disease

Transmission

In 1913 Townsend reached the conclusion, a priori that the insect vector was a sand fly, a Phlebotomus So certain did he feel of his inference, that he called the sand fly *Phlebotomus verrucarum* (Noguchi, Shannon, Tilden, and Tyler, 1928) Subsequent studies have confirmed his point of view Noguchi et al (1929) injected saline suspensions of crushed wild Phlebotomi, captured in the verruga zone, intradermally into rhesus monkeys, and in this way obtaine an infection in these animals The infection was detectable only by blood cu tures, which yielded positive cultures for *B bacilliformis* Similar results we obtained by Battistini (1929, 1931) Wild Phlebotomi collected in the endem area have given pure cultures of *B bacilliformis*, and, when fed on the monkeys, produced infections detectable by blood culture (Battistini 19 Hertig 1942) The sand flies selected for Hertig s experiments were *P v rucarum*

From the Peruvian verruga zone three species of Phlebotomi have bee scribed *P verrucarum* (Townsend, 1913) *P peruensis* (Shannon, 1929) *P noguchii* (Shannon 1929) Noguchi Shannon and associates thought the role as vector of *P noguchii* was certain that *P verrucarum* was a pro transmitting agent, and that the role of *P peruensis* was doubtful (Hertig (1942) however, believes that the females of Shannon s s material were predominantly *P verrucarum* Hertig with his exper and observations has demonstrated at least in the regions studied by hi the most important vector is *P verrucarum*

The degree of infection in Phlebotomi in natural conditions is a not yet answered It may probably vary from one place to another

The mechanism of transmission is through feeding In regard to of Bartonella in Phlebotomus, Hertig has been able to recover pure

in 1 case The same author states that in five patients who had not previously lived in "verruga" zones, the disease appeared after 19 to 30 days of residence in the infected area

For a better understanding, *it is desirable to describe separately the* two periods of the disease the noneruptive stage and the eruptive stage Within the first, the syndrome usually known as Oroya fever will be discussed

Noneruptive Stage

The clinical manifestations in the noneruptive stage vary from very severe cases in which high mortality is observed to cases in which symptoms are either absent or are very slight and can easily pass unrecognized In the latter, the so called noneruptive stage really does not exist (from the clinical standpoint), and thus the appearance of verrugas is the first observed symptom All intermediate cases may be found The severe case will be described first

OROYA FEVER

The onset may be acute with high fever reaching 40° C (104° F), chills and sweating, but more commonly, it is insidious, marked by malaise, headache, pains in the joints and long bones, and fever *A rapid,* progressive anemia develops from the beginning

As the disease progresses, the fever continues, and the anemia is more and more marked The skin and mucous membranes become pale The number *of red blood cells diminishes to less than two million per cubic millimeter,* sometimes to less than one million, and large numbers of Bartonellae are found in the erythrocytes The pains are severe The general state of the patient is poor The tongue is coated at the center, red at the point and edges There is anorexia, sometimes polydipsia nausea, vomiting, and *frequently diarrhea* Epistaxis and presence of petechiae in the skin are also frequent The arterial tension is low and the pulse is always accelerated, both in febrile and in apyretic periods Cardiac murmurs are often heard There is intense polypnea Commonly prostration is observed and the patient, *indifferent* to his surroundings may present delirium On the contrary, insomnia may occur The lymph nodes are enlarged The liver is commonly, but not always moderately hypertrophied In most cases the spleen is normal in size Complications such as paratyphoid infections have been reported

In fatal cases all symptoms are aggravated, the prostration increases insomnia is frequent, sometimes delirium occurs, the number of Bartonellae in the red cells is greater, anemia becomes more and more severe, diarrhea is always observed complications may appear—frequently pericarditis or a secondary infection—and the patient dies

The duration of these fatal cases is variable There are extremely acute cases in which death comes as early as the tenth day, but usually the fatal outcome is not observed until the third to the sixth week

In Jaramillo's series, death took place from the twenty first to the twenty sixth day in 4 cases, and at the fortieth day in 1 case (1939) In Groot's

Epidemics and Endemicity

In infected areas Carrion's disease remains endemic most of the time However, under certain circumstances the disease extends to neighboring zones especially after the rainy seasons It seems that most of the cases among natives, in endemic areas occur early in childhood and the incidence in adults is low However a large number of asymptomatic infections is observed It is significant to record that when people from a disease free region move to an endemic area—at least in Peru—they become infected sooner or later provided they remain unprotected from the bites of Phlebotomi Carrion's disease usually evolves in its most severe forms in these previously unexposed persons

Epidemics may occur when large numbers of previously unexposed people move into the endemic areas or when the disease extends to or appears in new territories Example of the former is the well known epidemic of 1870 in the Central Railway workers (see above) Recently in Colombia a very serious epidemic of Carrion s disease developed in zones where the disease had not been reported before (Patiño Camargo 1939) The epidemic began in 1936 reached its peak during 1938 1939 and 1940 and from 1941 began to subside slowly Up to September 1941 the infected area included the valleys and neighboring zones of the rivers Guáitara Juanambu Pacual and Mayo By the end of 1941 cases began to appear in Bolivar a somewhat isolated village about thirty miles north of the endemic zone and separated from this by a high (2 200 meters—7,200 feet—of altitude) chain of mountains This village because of such proximity had been permanently and carefully watched from the epidemiologic standpoint during the previous years No cases had been reported, but the presence of large numbers of Phlebotomi (species not identified) had been fully established The appearance of the disease in Bolivar apparently occurred after patients in the eruptive stage went to reside there

Under epidemic conditions there is no difference either in sex or age incidence The case fatality rate seems to be somewhat higher during epidemics than in endemic conditions

SYMPTOMATOLOGY

Incubation Period

The incubation period varies considerably In experimental human cases it has been from 16 to 21 days In the present discussion the end of the period of incubation is considered as the moment when the first clinical manifestations are observed and not from the presence of Bartonellae in the blood The author (1946) reported the case of a patient who developed Oroya fever 4 months after she had positive blood cultures for *B bacilliformis* The patient had been living in the endemic area for the last 3 years

Ricketts (1947) found in 7 cases which remained in endemic zones from only a few hours to 3 days the following incubation periods from 20 to 23 days in 4 cases 40 days in 1 case from 88 to 90 days in 1 case and 100 days

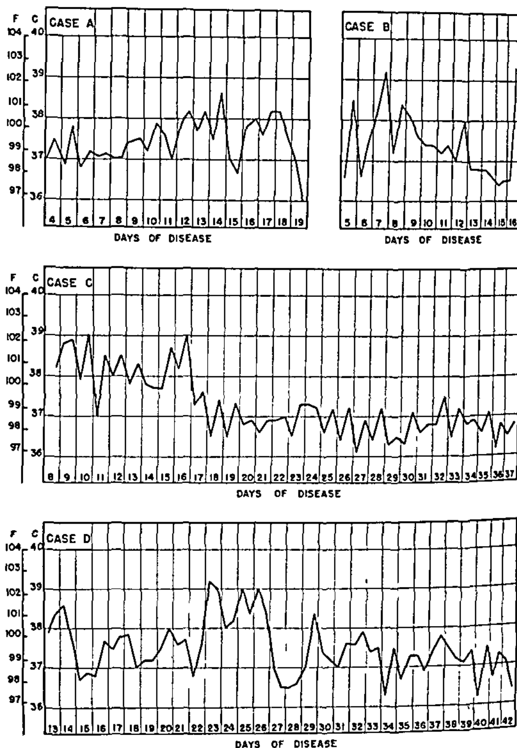


Fig 177 —Temperature charts of 4 patients with Oroya fever Patients *A* and *B* died Patients *C* and *D* recovered.

observations, death came from the fifteenth to the eighteenth day in 4 cases from the nineteenth day to the twenty second day in 4 cases, from the twenty seventh day to the thirtieth day in 2 cases and from the thirty eighth day to the forty sixth day in 4 cases

In cases which recover, after a variable period of 2 to 6 weeks, the fever decreases slowly, the Bartonellae disappear from the blood stream (as detected by films), sometimes quite suddenly There is an amelioration of all symptoms, pains decrease, the anemia ceases, and the number of erythrocytes begin to increase slowly The patient enters convalescence In certain cases the disappearance of the Bartonellae from the blood stream does not coincide with the cessation of the anemia (Hurtado et al, 1938) but it usually does

The rate of decrease in the percentage of infected red cells in most cases follows a similar trend

In favorable cases, infected erythrocytes are detectable by films for a period of time This finding varies in different patients in 3 cases reported by Jaramillo Bartonellae disappeared at the twenty seventh, twenty eighth, and thirty eighth day respectively, after the beginning of the disease, and in 5 cases studied by the author the disappearance occurred at the thirteenth, twenty third twenty fourth, twenty eighth, and forty eighth day, respectively

The end of Oroya fever is considered when the Bartonellae are no longer seen in the films, fever has disappeared, anemia is no longer being produced, and the number of erythrocytes has begun to increase

In most cases, and very often, when the patient has not recovered completely—1 to 2 months after the termination of the Oroya fever—the eruption of "verrugas" appears Apparently only in few cases does eruption not occur

Some Symptoms in Detail —

Fever —The fever follows no definite pattern and extreme variations are observed Generally it is of the intermittent or remittent type or a combination of both There is almost always a slight or marked evening exacerbation The difference between the morning and evening temperatures is usually not more than 1 5° C (2 7° F), but this may at times be 2° C (3 6° F) The remittent type seems to be more common In favorable cases, fever decreases slowly (in lysis) In fatal cases, death may come with high, normal or subnormal temperature The temperature rarely exceeds 40° C (104° F) Of 21 cases studied by the author, in only 3 were there exacerbations above 40° C In Jaramillo's series, out of 10 cases, only 1 showed more than 40° C The highest temperature is commonly between 38° an 39 5° C (100 4° and 103 1° F) The morning temperature may be normal, and usually is not above 38° C (100 4° F)

The Blood —From the beginning of the disease a rapid, progressive anemia develops Figures of about 1 000 000 red cells per cubic millimeter

are common The rate of decrease in the number of erythrocytes is quite rapid Sometimes as many as 300 000 red cells per cubic millimeter of blood are lost in twenty four hours *The volume, diameter, and thickness of the* red cells are greater than normal The mean hemoglobin concentration is usually low (Hurtado, Pons, and Merino, 1938), but it may be normal (Groot 1941) The blood volume is decreased especially when the anemia is very pronounced Hyperbilirubinemia is often observed but by no means is it constant The regenerative activity of the bone marrow is well marked and large numbers of reticulocytes and normoblasts are found in the peripheral blood *The number of these cells usually is proportional to the seriousness* of the anemia Quite often megaloblasts are found

The number of Bartonellae in the red cells varies Sometimes 99 per cent of the erythrocytes are infected, and it is possible to find ten to fifteen organisms in a single cell, but these are extreme cases Basophilic red cells and macrocytes are usually less infected Reticulocytes uncommonly present Bartonellae unless the number of microorganisms in the peripheral blood is very high Only in exceptional cases with a very high degree of parasitism are the microorganisms found in the normoblasts Bartonellae are seen some times in the cytoplasm of monocytes

Apparently destruction of the red cells is the fundamental cause of the anemia The mechanism of such destruction, however, remains completely obscure Production of hemolysins by the Bartonellae has never been demon strated in vitro or in vivo Direct action of the Bartonellae on the red cell and exaggerated erythrophagocytosis have been considered as possible, but definite proof is lacking

Leucopenia may be observed at the beginning of the disease It is *generally accepted that in uncomplicated cases* the number of leucocytes is customarily normal (Hurtado, 1938) In 19 cases in which blood counts were performed almost daily during the course of the disease, the author has ob served in 13 cases normal counts throughout the entire course of the disease in 3 cases, normal values throughout the course of the disease *with slight* leucocytosis during convalescence, and in 3 cases, occasional slight leuco cytosis, with normal values most of the time

The differential count is not typical It is possible to find either a very slight lymphocytosis or, more commonly, polymorphonucleosis

During the period of severe anemia, there is always an increase in young polymorphonuclears and younger cells of the myeloid series

The sedimentation rate is markedly increased, giving values between 100 and 172 mm in 1 hour with the Westergren method Making the correction for the degree of anemia, values from 85 to 120 mm in 1 hour are usually *found The Gaté Papacostas formol* gel test is sometimes positive as well as the flocculation of serum globulin with distilled water (Groot, Mayoral, and Martinez, 1941)

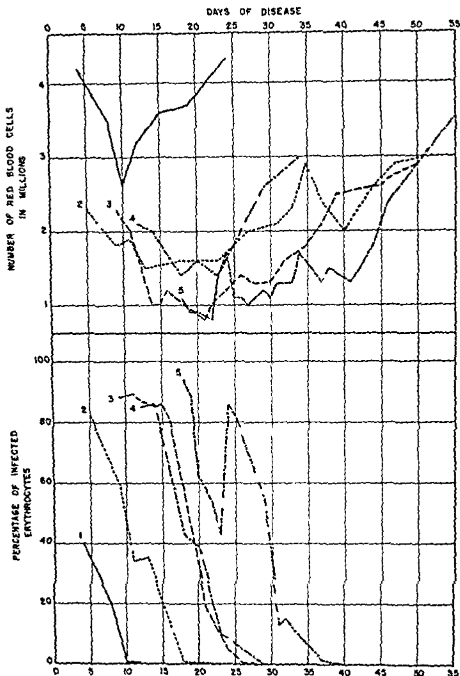


Fig 179.—Red blood cell counts made at frequent intervals with associated percentages of infected cells in 5 untreated recovered cases of Oroya fever

mal Weiss (1932) has described cases in which the appearance of verrugas took place 18 months later and frequently periods of 6 to 10 months have been recorded In (2), conditions similar to those of (1) occur In (3) the constitutional symptoms may precede the eruption for *only a few days and these symptoms* may be exacerbated at the beginning of the eruption to recede completely shortly thereafter The incidence of (4) seems to be not rare Such an occurrence was observed by the author in 9 out of 42 verruga cases in epidemic conditions



Fig 179 —Human bartonellosis eruptive stage Disseminated miliary and nodular lesions of the face Palpebral conjunctiva of the right eye with verrugas Most of the lesions were pink or bright red The patient still shows emaciation due to the preceding attack of Oroya fever

In the eruptive stage the lesions may develop from (1) the superficial layers of the skin and certain mucosae (2) the deep layers of the skin and (3) the subcutaneous tissue Verrugas in (1) usually small are designated as *miliary , verrugas in (2) and (3) as nodular Miliary lesions are* small 1 to 3 mm in diameter or somewhat larger 7 to 8 mm They are round raised hemispheric red or cherry colored covered with a thin layer of shiny skin sharply circumscribed from the surrounding tissue which presents no sign of inflammation Early in their evolution verrugas which grow in the deeper layers of the skin give upon palpation the sensation of a hard nodule later they appear at the surface of the skin The lesions which develop in the subcutaneous tissue at first appear as hard nodules which may reach a size of several

The occurrence of autoagglutinins seems to be rare Monge described some cases and the author had the opportunity of finding 1 case in a series of 26 patients

Pain—Pain is always present and may be the first observed symptom Often it persists during the convalescence The pains are located most commonly in the joints—hands feet knees ankles—and in the epiphyses of the long bones Pressure on the bones may be painful or may exaggerate an already existing pain These pains may be intermittent Rachialgia is frequently observed Headache is quite common and is almost always constant

Nervous Symptoms—Among the most common symptoms usually reported are dizziness and vertigo Insomnia is frequent Delirium often occurs especially just before death and in such cases carphologic movements may be observed Convulsions have been reported but it seems that they are not usual

Urine—The urine is usually concentrated and dark amber in color It may contain small amounts of albumin usually not more than 0 20 Gm per liter and some hyaline and granular casts Urobilinogen is commonly increased

MILD CASES

Numerous cases show only a mild symptomatology for a few days to weeks or even a month or more of duration characterized principally by slight and occasional fever malaise arthralgias, often moderate anemia In these cases small numbers of Bartonellae may be seen in blood films or the microorganism may be demonstrated only by blood cultures Ordinarily these patients do not need to interrupt their usual occupations or remain in bed The eruption of verrugas may take place when such constitutional symptoms are still present When this is the case the fever usually mounts and the joint and bone pains are markedly increased In other cases this vague symptomatology subsides and after a variable period of time the eruption appears

On the other hand the clinical manifestations may be absent or so mild that they pass unrecognized

Eruptive Stage

The eruptive stage is characterized clinically by the appearance of small hemangioma like tumors in the skin and subcutaneous nodules In most cases constitutional symptoms of variable intensity such as fever and arthralgias are present at the beginning of the eruption

Verrugas may appear (1) after a previous attack of Oroya fever (2) when the patient has presented some time before mild symptoms of the non eruptive stage of the disease (3) when the patient has been presenting mild constitutional symptoms in the days or weeks immediately prior and still presents them and (4) when the patient gives no history of previous disease is apparently in good health and cannot recall any particular symptom in the preceding days or months In (1) verrugas usually appear from 2 to 8 weeks after the remission of the anemia when the patient is still convalescing from the previous attack of Oroya fever and the number of red blood cells is not yet nor

centimeters The nodule adheres to and raises the covering integument and at this point may regress without causing further pathologic changes, except sometimes the reddening of the skin, or, on the other hand they may erode the skin, reach the surface, and appear then as red tumors with irregular contours frequently pediculated Such tumors are usually designated as verruga of the "mulaire" type

Miliary lesions may appear anywhere in the skin or in the mucous membranes of the mouth, nose, and eye, although they are more frequent in the face and limbs They may be few in number, or, on the other hand, extremely numerous disseminated throughout the surface of the body Benavides (1942) reported a case with 1,272 eruptive elements



Fig 189—Human bartonellosis eruptive stage Large verruga of the mulaire type

Nodular and tumor lesions ("mulaire") are far less numerous than miliary verrugas Subcutaneous nodules often appear near the elbows and the knees where they are usually painful and may cause functional disturbance of the limbs

Verrugas bleed easily, and some of them may appear to be covered by a blood crust "Mulaire" lesions are especially prone to bleed and are almost always secondarily infected

The duration of the eruption varies It may persist from 1 month to 2 years (Odriozola, 1898), but usually it lasts 1 to 6 months In Jaramillo's series



Fig 180.—Human bartonellosis, eruptive stage. Two verrugas of the ear



Fig 181.—Human bartonellosis, eruptive stage. Large verruga of the left cheek.

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the duration of the eruptive stage was 7 weeks in 2 cases 8 weeks in 1 case, 9 weeks in 1 case 12 weeks in 2 cases and 20 weeks in 1 case (1939)

Frequently the eruptive elements appear in successive outbreaks so that it is possible to find in the patient verrugas in different phases of evolution The lesions heal without leaving a scar unless they have been secondarily infected

The preceding description does not cover all the observable clinical cases but it certainly applies to the large majority Odriozola described some cases in which Oroya fever followed the eruptive stage Likewise forms with mild symptomatology and marked rheumatoid pains which persist for months or years and which cease with the eruption of verrugas have been reported as well as cases of long duration in which the principal symptom was the repeated appearance of discrete eruptive lesions

IMMUNITY

People who have had the disease and continue to live in endemic areas in most cases do not present second attacks of Carrión's disease Certainly some cases of repeated attacks of verruga have been reported but they are far from common This leads us to think that in most cases a lasting immunity develops after the disease From experimental data we know also that monkeys show resistance to reinoculations

The numerous cases in which Bartonellae are found in the blood long after recovery from the disease indicate that the immunity which usually follows the clinical attack coexists at least in some cases with latent infection and the presence of Bartonellae in healthy people without previous history of the disease shows that in these cases there is a balance between the infected man who cannot eradicate his infection and the infective agent which does not cause apparent disturbances in its host This balance may be disturbed with the consequent development of Carrión's disease in the carrier or possibly it may not be disturbed but the infection may remain completely asymptomatic throughout its course This condition is similar to the state of premunition which exists in animal bartonellosis In rats infected with *Haemobartonella muris* the infection usually remains asymptomatic but when such rats are splenectomized the latent infection is changed into apparent disease This may occur also when rats are secondarily infected with several species of Salmonellae and Pasteurellae or when combined A and C avitaminoses are produced in the infected rodents

The duration of the latent infection following the disease has not yet been established however it may be long Mackehenie (1934) reported a case of an engineer who gave positive cultures 16 months after an attack of verruga and a patient with nervous symptoms who 6 months later yielded pure cultures of *B bacilliformis* Howe (1943a) obtained positive blood cultures from a person who had had the disease 5 years previously Most of these postconvalescent asymptomatic infections have been reported from people living in the endemic zone so that it is impossible to evaluate whether such cases represent single or repeated infections Postconvalescent asymptomatic infections may become apparent even after long periods of time although such cases appear to be ex

tremely rare Escomel (in Weinman 1944) reports a case of a patient who had had an attack of verruga then lived in Europe for 20 years upon his return to Peru and before he had passed through any known endemic zone a tumor developed on his toe this was a typical verruga with numerous demonstrable Bartonellae The patient stated that during his residence in Europe he had had similar tumors

Howe (1942 1943a) demonstrated the presence of specific agglutinins in the blood in cases during or after the disease In the noneruptive stages titers as high as 1 160 but usually 1 20 were found During the eruptive stage titers ranged from 1 80 to 1 320

PATHOLOGIC ANATOMY

Oroya Fever

Fatal cases of Oroya fever show at autopsy signs of an advanced anemia There is usually marked emaciation Disseminated petechiae may be observed in the subcutaneous tissue The lymph nodes are moderately but clearly en larged and when cut appear pink or reddish The spleen may be normal

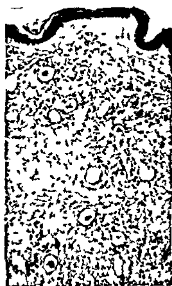


Fig 183 —Skin biopsy in Oroya fever showing cellular infiltration and vessels with agglo merates of *Bartonella bacilliformis* (Courtesy of Oscar Felsenfeld)

or slightly enlarged and may show numerous infarcts (Strong et al 1915) Hepatomegaly is sometimes observed Frequently the pericardium con tains a large amount of fluid serous in appearance (Groot et al 1941 Wein man 1944) Disseminated hemorrhagic petechiae may be found in different viscera

Microscopically besides the presence of Bartonellae in the red blood cells the most striking finding is the lesion observed in cells of the reticuloendothelial system The lesion consists of the development of Bartonellae within the cyto

the duration of the eruptive stage was 7 weeks in 2 cases, 8 weeks in 1 case, 9 weeks in 1 case, 12 weeks in 2 cases, and 20 weeks in 1 case (1939)

Frequently the eruptive elements appear in successive outbreaks, so that it is possible to find in the patient verrugas in different phases of evolution. The lesions heal without leaving a scar unless they have been secondarily infected.

The preceding description does not cover all the observable clinical cases, but it certainly applies to the large majority. Odriozola described some cases in which Oroya fever followed the eruptive stage. Likewise, forms with mild symptomatology and marked rheumatoid pains, which persist for months or years and which cease with the eruption of verrugas, have been reported, as well as cases of long duration in which the principal symptom was the repeated appearance of discrete eruptive lesions.

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People who have had the disease and continue to live in endemic areas in most cases do not present second attacks of Carrión's disease. Certainly some cases of repeated attacks of verruga have been reported, but they are far from common. This leads us to think that in most cases a lasting immunity develops after the disease. From experimental data we know also that monkeys show resistance to reinoculations.

The numerous cases in which Bartonellae are found in the blood long after recovery from the disease indicate that the immunity which usually follows the clinical attack coexists, at least in some cases, with latent infection, and the presence of Bartonellae in healthy people without previous history of the disease shows that in these cases there is a balance between the infected man who cannot eradicate his infection and the infective agent which does not cause apparent disturbances in its host. This balance may be disturbed with the consequent development of Carrion's disease in the carrier, or, possibly, it may not be disturbed but the infection may remain completely asymptomatic throughout its course. This condition is similar to the state of premunition which exists in animal bartonellosis. In rats infected with *Haemobartonella muris*, the infection usually remains asymptomatic, but when such rats are splenectomized, the latent infection is changed into apparent disease. This may occur also when rats are secondarily infected with several species of Salmonellae and Pasteurellae, or when combined A and C avitaminoses are produced in the infected rodents.

The duration of the latent infection following the disease has not yet been established, however, it may be long. Mackehenie (1934) reported a case of an engineer who gave positive cultures 16 months after an attack of verruga, and a patient with "nervous symptoms" who, 6 months later, yielded pure cultures of *B bacilliformis*. Howe (1943a) obtained positive blood cultures from a person who had had the disease 5 years previously. Most of these postconvalescent asymptomatic infections have been reported from people living in the endemic zone, so that it is impossible to evaluate whether such cases represent single or repeated infections. Postconvalescent asymptomatic infections may become apparent even after long periods of time, although such cases appear to be ex-

are congested, with dilated sinuses Strong (1915) has reported ulcerations in the large intestine with distinct undermining of the mucosa at the edges These lesions occurred near capillaries with numerous infected endothelial cells

Eruptive Stage (Verruga)

The lesion consists of newly formed vessels of different sizes lying in connective tissue, with edematous zones, hemorrhagic foci, and a marked proliferation of the endothelial cells of the vessels Bartonellae are present in these proliferated cells They are rod shaped or form round masses However, these clusters are never as pronounced as in the organs in Oroya fever cases, and the distention of the infected cells is significantly less common than in Oroya fever (Pinkerton and Weinman, 1937) The epithelial cover of the verruga is thin

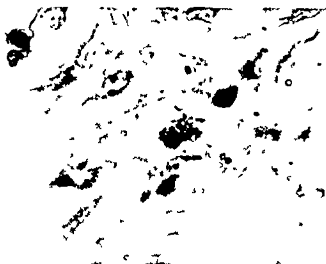


Fig 185—Section of a verruga *Bartonella bacilliformis* within the protoplasm of a macrophage Giemsa stain (×1280) (Photograph by C Sanmartin)

sometimes with signs of parakeratosis (Groot, Mayoral, and Martinez, 1941), and may be absent in some places, in which case it is replaced by a layer of fibrin and leucocytes At the periphery of the lesion the capillaries may be markedly dilated As the lesion progresses the connective tissue becomes more abundant and in some cases may present a fibrosarcomatous appearance When the verruga becomes older, the fibroblasts and the collagen fibrils increase in number The epithelial cover may be hypertrophied, and portions of cornified epithelium may be seen in the depth of the connective tissue mass (Strong, 1915, Groot et al, 1941) When secondarily infected, the lesions develop purulent foci

The histology of the subcutaneous nodules is similar to that of the cutaneous lesions The subcutaneous nodule is usually surrounded by a connective tissue capsule which sometimes sends thin walls into the mass of the lesion In its center, foci of necrosis may be found (Groot et al, 1941)

plasm of endothelial cells of sinusoids and of lymph and blood capillaries (Strong et al, 1915) Infected cells have been found in the lymph nodes, in the liver, bone marrow, spleen, kidney, intestines, adrenals, pancreas, in the skin, and occasionally in the heart and lung (Weinman, 1944) In the infected cells the Bartonellae sometimes are discrete and rod shaped as seen in more than 80 per cent of infected Kupffer cells of the liver (Pinkerton and Weinman, 1937), but in the remaining 20 per cent and in all other organs the microorganisms appear aggregated in granular or amorphous spheroidal masses which distend the cells, sometimes to an extreme degree Marked erythrophagocytosis by the Kupffer cells of the liver and the macrophages of the spleen is observed These cells also contain hemosiderin (Ash and Spitz, 1945)



Fig 184 —Section of a verruga. Hematoxylin eosin stain Low power (Photograph by C Sanmartin)

The liver presents areas of necrosis of the central type about the hepatic vein (Strong et al, 1915) Hurtado, Pons, and Merino (1938) have reported degeneration also around the central veins According to Weinman (1944), it is likely that such necroses are due to anoxemia Strong attributed them to a probable toxin, not yet isolated The spleen is congested, with infarcts, venous thromboses, marked erythrophagocytosis, and large amounts of pigment, yellow or yellowish brown, present within the macrophages as well as in free masses outside the cells This pigment does not give the iron reaction The bone marrow shows functional hyperactivity, that is, a transformation to red marrow of a great part of the yellow marrow of the long bones The enlarged lymph nodes

symptoms are low blood pressure, extreme tachycardia normal temperature with large numbers of Bartonellae in the blood, the appearance of complications such as pneumonia or salmonellosis, and the marked increase of urobilinogen in the urine The daily examination of the blood gives very useful data about the course of the disease and its possible termination Generally the degree of anemia is proportional to the seriousness of the prognosis, and a small number of reticulocytes is unfavorable The appearance of eosinophiles is usually considered as a good prognostic sign (Hurtado et al, 1938, Groot et al, 1941)

During the eruptive stage, recovery is the rule However, Odriozola (1898) has described some cases in which Oroya fever followed the appearance of verrugas, but such cases seem to be extremely rare In Colombia no deaths have been reported during the eruptive stage

TREATMENT

Several drugs have been used in the treatment of Oroya fever, almost always without significant beneficial effects Neoarsphenamine, Prontosil, sulfanilamide, sulfapyridine, neutral salts of acriflavin, quinine have not proved successful SDT 386, a Bayer arsenic and antimony compound, which has given good results in *Haemobartonella muris* infection of rats, is useless in Carrion's disease

Recently penicillin has been used Although the present data are not conclusive, there is some evidence that this antibiotic is helpful, at least in certain cases Castro (1945, 1946) treated 59 Oroya fever patients with doses between 100,000 and 2,000,000 units He states that in most cases there was a notable amelioration of the symptoms after the treatment Among the 59 patients, 10 died Castro has found a mortality of 40 per cent in untreated cases Aldana (1945, 1946), Aldana and Tisnado (1945), Robinson (1945), Vila y Acuña (1945), and Merino (1945) employed total doses ranging from 240 000 to 1,600,000 units, using a daily dose between 100,000 and 200 000 units Most of the patients received a total of 600,000 units When the treatment was begun, 13 patients had a marked degree of anemia Of their 14 Oroya fever patients, 3 died 1 because of a pneumonia complication, and 2 who were received for treatment with very severe anemia and in a markedly poor condition The authors report significant improvement of the clinical condition in the remaining 11 One of these 11, however, later developed salmonellosis and died The element of fever was improved in most cases and a marked drop in the number of Bartonellae in the peripheral blood was observed 8 to 72 hours after initiation of treatment Seven months after the penicillin treatment, none of the recovered patients had developed verrugas The number of these observations is small, however, the results seem encouraging

Howe (1943b) treated 3 cases with immune rabbit serum In such cases the degree of reduction of Bartonellae in the blood stream was more rapid than in the controls In 1 case the time in which the eruptive stage appeared after Oroya fever had receded was notably short

Weinman (1944) found in sections of apparently normal skin from a case of Oroya fever proliferated and infected endothelial cells together with large numbers of capillaries. The lesion thus appeared as the possible beginning of a verruga.

DIAGNOSIS

Noneruptive Stage

Demonstration of the causative agent in the peripheral blood makes the diagnosis and is essential for such a diagnosis. The procedures usually followed are the microscopic examination of stained films, both thin and thick, and when necessary, blood cultures in suitable media. When the disease is well established, the irregular fever, the rapid and severe anemia, the high erythrocytic sedimentation rate, the pains in the joints, the enlargement of the lymph nodes, the environment in which the patient has recently lived are all data of great value for a diagnosis.

However, early in the disease or when the disease runs a very mild course, the clinical manifestations are by no means marked and the Bartonellae might not be found by microscopic examination of the blood. In these cases it is necessary to make blood cultures. For this purpose the medium which has given the best results in the hands of the author is Geiman's semisolid medium (see above).

Eruptive Stage

The appearance of the verrugas is so characteristic that it is difficult to mistake the disease for any other. The clinical diagnosis may be confirmed by demonstration of the Bartonellae in the lesions. Sections should be prepared with Regaud's fixative stained later with Giemsa stain. The verruga may resemble an angioma, an angiofibroma or a botryomycoma. These tumors, however, are almost always single and congenital. Bassewitz described in Brazil "angiofibroma cutis circumscriptum contagiosum," a condition similar to verruga. So far the true nature of Bassewitz tumors has not been established and from present data there is not sufficient information on which to base a differential diagnosis.

The subcutaneous nodules, when they have not eroded the skin, may resemble fatty tumors, fibromata and similar pathologic conditions. However, the coexistence with typical miliary verrugas, the localization near the joints and the course of the disease furnish the diagnosis. In doubtful cases bacteriologic and histologic study of the lesions should be made.

In this period blood cultures are often positive.

The disease is not transmissible to the usual laboratory animals. Even monkeys are difficult to infect.

PROGNOSIS

When a patient presents the Oroya fever syndrome, prognosis is not good. The mortality in such cases is high, about 40 per cent. The individual prognosis depends upon the general state of the patient. Among bad prognostic

with a similarly prepared vaccine, 44 children in the village of Bolivar (Colombia) The vaccinated children and 45 unvaccinated controls were watched during the following 3 years Two cases of Carrion's disease were observed among the vaccinated individuals, and 6 cases among the controls During those 3 years, 10 per cent of the entire population of Bolivar presented Carrion's disease

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Good nursing care and well balanced and adequate diet are essential The administration of ferrous sulfate liver extracts vitamins B_1 and C is usually recommended as accessory measures Blood transfusions are indicated especially when the anemia is marked These transfusions should be large and should be repeated frequently

The therapeutic measures during the eruptive stage tend to maintain the patient in good condition Care must be taken to prevent secondary infection of the verrugas Excision sometimes is indicated When this is the case it is preferable to await full growth before operating This occurs when the verrugas near the joints cause limitation of function of the limbs or when the lesions become gangrenous Vila y Acuna (1945) and Aldana and Tisnado (1946) have reported three cases of verrugas treated with penicillin They report that a marked improvement of the condition is observed and that the treatment hastens the improvement of the lesions One of the cases was treated after 4 months of development and cure was reported 2 weeks later In the second case after approximately 15 days of development treatment was given over 11 days and a few days later the patient was discharged with notable improvement In the third case after a period of 28 to 58 days the patient was treated for 10 days at the end of which many lesions had totally disappeared and no new eruptive elements had appeared

PROPHYLAXIS

From a theoretical standpoint 3 kinds of prophylactic and control measures might be considered (1) those intended to prevent Phlebotomi from biting man (2) those intended to destroy the insect vector (3) prophylactic immunization

In regard to the first staying after dusk only in Phlebotomus proof houses and departure from the endemic zone at night have been suggested To reduce sand flies DDT has been used recently and appears promising Hertig and Fisher (1945) found this insecticide effective against Phlebotomi in Italy and in the Dead Sea area Unfinished experiments in Colombia performed by Mondragon on a wide scale in two villages in the endemic area have shown so far a significant decrease in bartonellosis morbidity rate after the application of DDT

As far as prophylactic immunization is concerned the search for a possible effective vaccine has begun Very limited experiments have been performed though and the results cannot be considered as conclusive Howe and Hertig (1943) vaccinated a group of 22 previously unexposed volunteers who intended to establish residence in a highly endemic district The vaccine consisted of injection of a formol killed suspension of *B bacilliformis* which had been grown in German solid medium Out of the 22 volunteers 19 developed specific agglutinins with titers up to 1 160 after the vaccination After a variable time of residence in the verruga zone 12 of the vaccinated persons had positive blood cultures for *B bacilliformis* and developed mild systemic symptoms, such as slight fever arthralgias and headache Only one of these 12 patients had to be hospitalized but 5 later showed eruption of verrugas. The author vaccinated

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latitude south where the average yearly temperature is 70° F The disease is almost unknown in the regions beyond 35 to 40 degrees N and 20 degrees S, although 160 cases have been recorded by Lichtman (1947) in Durban, Natal, Union of South Africa, at 30 degrees S There are very few cases above an altitude of 1500 feet above sea level The countries where ulcers have been found are given below

Equatorial Africa—Gold Coast, Kenya, Mozambique, Sierra Leone, Liberia, Gambia, Nigeria, Northern Rhodesia, Oran, Nyasaland, Tanganyika, Uganda, Sudan, Zambezi, Algeria, Belgian Congo, Somaliland, Tripoli, Libya, and Madagascar

Central and South America—British Guiana, San Domingo, Jamaica, Trinidad, Argentina, and Brazil

Asia—Syria, Aden, Israeli, Persia, Red Sea Islands, India, Burma, Federated Malay States, Yemen, Java, Siam, *Singapore, Indonesia, Indo China, Melanesia, Philippine Islands,* New Guinea, and southern China

Europe—Caucasia

In many tea districts of Assam and Cachar in India, the disease is endemic, occurring almost every year and sometimes in an epidemic form

Hughes states that in Assam, India, 35 to 40 per cent of the labor population in the tea gardens is temporarily disabled Charters (1947) found, among 292 Somali soldiers admitted, no less than 143 affected with tropical ulcer Grenoilleau (1946) actually recorded 7,923 cases in 1943 and thought that there were likely to be 57,401 actual cases Though the diagnosis of all kinds of ulcers is not given, there is little doubt that the majority belonged to the phagedenic type According to Manson Bahr (1940), the ulcer is a great scourge in the Solomon Islands and indeed in the whole of Melanesia

It is clear from all these records that the disease is important from the standpoint of public health

Season and Epidemiology

Most cases occur when the weather is hot and humid Clements (1936) noted the highest incidence in New Guinea towards the end of the rainy season when the soil was still damp Roy (1928) records the maximum incidence in July in Assam, when there is usually *very heavy rain Abundant rainfall and warm and damp soil are favorable factors* Panja (1945) noted in July to December of 1943 a large number of cases occurring in Calcutta. Grenoilleau (1946) records an epidemic beginning in July and subsiding at the end of December He goes on to state that the seasonal character of the disease is of an estivo autumnal type

Pattanayak (1944) notes the highest peak in August and September, whereas Nath (1946) finds the highest incidence in October to December Luthra (1946) found cases for 2 months after the rains in the Punjab

From a consideration of all the data, it is evident that the epidemic is prevalent in the rainy season and for 2 to 3 months in the postmonsoon period, and it gradually disappears as winter approaches There is one peculiarity in the epidemiology of the disease It is endemic in certain localities, for example, Assam in India, whence the epidemic spreads in some years Cases were unknown in Bengal for many years, but in 1943 an epidemic spread not only in Bengal but almost all over India including Bombay, Gujrat, Madras, Central Provinces, Orissa, and Punjab, etc As usual, there is also a periodicity in the epidemic There were many [illegible]
in 1943 to 1946 I [illegible]
through the end of [illegible]
average daily 50 admissions into hospitals was recorded, the highest peak was in the middle of October In fact, the disease affected the population, including Europeans, especially the womenfolk, to such a degree that it amounted to a veritable scourge (Grenoilleau, 1946) In some years in Assam, according to Hughes (1931), as already stated, 35 to 40 per cent of the coolie population is affected in the tea gardens at Sylhet Roy (1928) records average duration of absence from duty in a year in a garden at Sylhet at 41 4 days and consequently

CHAPTER 33

TROPICAL PHAGEDENIC ULCER (VINCENT'S ULCER)

GANAPATI PANJA

Synonyms.—Ulcus tropicum, tropical ulcer, Naga sore (Assam, India), Cachar boil, Malabar ulcer, Jungle Ghao, Gala (Gwalior, India) Annam ulcer, Cochin sore, Aden ulcer, Yemen ulcer, Mozambique ulcer, Delago sore, Natal sore, Rhodesian sore, Zambesi sore, tropischer phagedenismus (German), Ulcère phagédenique des pays chauds (French), Goyana ulcer, Chaco ulcer (Argentina), Tropical sloughing phagedaena

The best name should be either "tropical phagedenic ulcer" or Vincent's ulcer, as the word "phagedenic" means 'eating canker" and such a phagedenic condition with presence of copious slough and Vincent's fusiform bacilli is characteristic of the ulcer

The simple name "tropical ulcer" is misleading as there are, in the tropics, many ulcers free from phagedena and fusiform bacilli Tropical ulcers described by Golden and Padilla (1946) at Guatemala are not the phagedenic ulcers There is no exudate in a 2 week old ulcer and no fusiform bacilli found in any case

Ulcers described by Dostrovsky and Sagher (1946) at Palestine are probably not tropical phagedenic ulcers These are neither oval nor circular are surrounded by superficial detachment of epidermis, and are free from fusiform bacilli

There are sloughing ulcers in the tropics but without any fusiform bacilli These are not tropical phagedenic ulcers Hence the very best name should be Vincent's ulcer Costa (1944) has also suggested the same name

The earliest record of the disease is found in a Burma expedition recorded in James Annesley's *Researches Into the Cause, Nature and Treatment of the More Prevalent Diseases of India* (1828) The disease was known in Algiers (North Africa) in 1896

DEFINITION

It is an acute specific ulcer, single or multiple, circular or oval, punched out and excavated, with indurated and raised borders varying in size from 1/4 to 2½ inches in diameter confined mostly to the lower legs feet and toes, associated with copious and often fetid pus, tenacious slough, sero sanguineous discharge pain and a tenderness and rarely accompanied by enlarged neighboring glands fever, and constitutional symptoms The ulcer develops later into a chronic stage without the foregoing typical features

ETIOLOGY

Geographic Distribution and Incidence

This has been well shown by Clements (1936) It is very interesting to note that the ulcer is found more often near the Equator in tropical and subtropical countries that are included in a belt drawn around the globe between the 35th latitude north and the 10th

on the disease are unanimous in acclaiming trauma as being the starting point in most cases Trauma or skin disease also reduces the reduction potential of tissues and thus favors the development of a sore by subsequent infection

Diet

Much attention has been paid to diet as being the possible cause of the disease Some workers regard general malnutrition as an essential factor

McCulloch et al (1928) and Brown (1935) laid the etiology on low protein and fat high carbohydrate, and inadequate vitamin supply Clements (1936) carried on a careful observation of the diet in New Guinea and came to the conclusion that deficiency of the vitamin B complex associated with diet rich in carbohydrates but low in protein and fat was undoubtedly a predisposing factor Farle (1942), on the other hand, thought nicotinic acid was the important factor Almost similar results were obtained by Orr and Gilks (1931) in East Africa and Burnie (1931) in Nigeria Edge (1921) considered the condition to be a deficiency disease Scott (1941) and Charters (1943) laid stress on deficiency in vitamin A as being the precursor of the production in tropical ulcer The latter tested improvements in ulcers by giving calcium, codliver oil, and milk, and comparing results with a control group, but his number of cases was so small that no statistical significance can be attached to his results Corkill (1939) also does not agree with his results and says that vitamin A improves the rate of healing of many kinds of ulcers Moreover, it has been found that healing takes place in an average number of 45 days when vitamin A is given and at the same time the ulcers are dressed with codliver oil In the control group, however, when the ulcers are only dressed with zipp and no vitamin given, the average number of days is less, that is, 39 days Blank (1947) was of the opinion that vitamin B deficiency was an important predisposing cause and called the malady a "poor man's disease" Lichtman (1947), in Natal, considered the condition to be mainly nutritional in origin He found the disease strikingly seasonal In autumn, the diet of the people consisted mainly of maize and the disease was in its highest peak in May, but in winter people had cattle flesh as well with the result that the disease disappeared Calcium deficiency has been cited by Brown (1935) and Loewenthal (1932) as an important predisposing cause Brown found daily intravenous calcium chloride definitely beneficial Loewenthal gave intravenous calcium chloride, 15 grains in 10 c.c of distilled water daily, and found 52 per cent cured and 32 per cent improved On the other hand, Brown (1935), Clements (1936), and Farle (1942) did not find any deficiency in calcium in the blood

It may be stated here that if calcium deficiency or malnutrition is the important cause, these questions arise Why do the ulcers occur mainly on the lower legs? Why does penicillin cure all cases even if associated conditions are neglected? There are many other workers who have strong reasons to believe that malnutrition is not the important cause

Patterson (1908), with his wide experience, found the disease in healthy persons as well Buchanan and Sanderson (1935), in Africa, found no favorable response to diet rich in vitamins Hughes (1931) noted no improvement by feeding with codliver oil, orange juice, and yeasts Marsh and Wilson (1945) remarked that most of their cases healed even though slowly, in spite of their dietetic errors In Panja's (1945) series of 61 cases, malnutrition was noted in but 4 cases, 57 cases were in good health

The author's position is based upon the following facts

1 The disease was not seen in Calcutta for years prior to the epidemic of 1943 although dietetic deficiency had long been common

2 The disease was seasonal and the epidemic subsided in spite of the prevailing dietary deficiency

a great economic loss is sustained by the tea garden companies Patterson (1908) remarked "This year the typical phagedenic ulcers have swept like a plague up the whole of Assam on both banks of the Brahmaputra River and have temporarily incapacitated many thousands of coolies "

Age

The disease is common in young adults engaged in active occupation Roy (1928) records the disease in 99 6 per cent of adults and 0 4 per cent of children and infants Ghose (1934) found the disease in only 3 children out of 69 cases In the Calcutta epidemic recorded by Panja (1945) no young children and infants were found affected Clements (1936) notes the highest incidence in ages 10 to 40 among 250 cases studied and remarks that children under 5 years are scarcely affected Pandit (1946) writes that the largest number of patients falls in the age group of 10 to 30 years

From all these records it can be concluded that the largest number of victims falls in the age group of 10 to 36 years Cases are extremely rare below the age of 5 and old people are scarcely affected

Sex

The disease has a higher incidence in males, and it may be 6 times more frequent than in females

It is interesting to note that in certain tea gardens of Assam the female population is more often affected This might be due to the fact that the laboring population in those gardens consists of a preponderance of females Grenouilleau (1946) in Algeria, records women victims more often among 85% European cases and suggests bare legs (without stockings) as being the predisposing cause of infection

Occupation and Nationality

Occupation is a very important predisposing cause Barefooted laboring classes are the most frequent victims in the tea gardens of India Hughes states that in Assam 35 to 40 per cent of the labor population is temporarily disabled during the busiest season of the year This fact alone suggests the possibility of an infection attacking the legs from the soil Besides occupation leads often to trauma which favors the entry of infection as will be shown later on Europeans are not barefooted and do not go about in the mud It is mainly for this reason that they are very rarely affected In India not a single case among Europeans is recorded although they are in close association with the labor population in the tea gardens. The better class Indians who have clean habits wear shoes and do not work in the fields escape the disease As stated above Grenouilleau (1946) in Africa recorded many cases among Europeans especially women The reason put forward by him is that women although they wear shoes have their lower legs exposed to insect bites scratches etc and this allows entrance of infection from the soil

Trauma

Trauma is a very important predisposing cause and may take the form of abrasions cuts puncture wounds mosquito or leech bites, burns injection thorn pricks smallpox vaccination or skin diseases such as impetigo boils, pustules trophic ulcers of leprosy etc Most of the cases give history of trauma in some form or other It has also been proved experimentally that trauma is necessary for the production of a sore

Clements (1936) in his series of 179 cases found sores in 114 cases definitely traumatic in origin Burnie (1931 in 250 cases noted ulcers occurring at the sites of injury in 244 cases Fox (1932) found sores developing at the sites of inoculation of cholera vaccine in 14 coolies Blanchard (1914) recorded ulcers on vaccination pustules Almost all the writers

BACTERIOLOGY

The bacteriology of this disease has been studied in detail by a number of workers When a film of pus from a typical ulcer is examined from day to day by staining with Gram's Leishman's, Giemsa's, and Ziehl Neelsen's stains, gram positive fusiform bacilli are always found Vincent's spirochetes are found in some ulcers Gram positive cocci, diphtheroids, and gram negative bacilli are sometimes found No acid fast bacilli or protozoa are seen

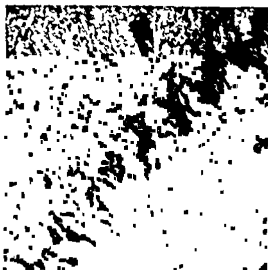


Fig 186 —Section of Naga sore showing the row of fusiform bacilli in the depth of the ulcer

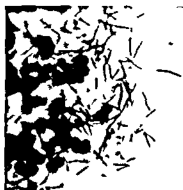


Fig 187 —Smear from Naga sore showing fusiform bacilli

It is claimed that Le Dantec (1884) was the first to find the Vincent bacillus (fusiform bacillus) Vincent (1896) found fusiform bacillus and spirillum in 40 out of 47 Arabian tourists suffering from the disease Blanchard (1905) and von Prowazek (1907) attributed the cause of the ulcers to the spirochetes Noguchi considered the spirochete to be the same as *Treponema vincenti* Keysselitz and Mayer (1909), working in Africa, were perhaps the first to describe fully the fusiform bacilli and the spirochetes Apostolides (1922), in Smyrna, studied 202 cases and was of the opinion that the only causative agent, the sine qua non of tropical ulcer, was the fusiform bacillus in association with *Spirochaeta schaudinni* Roy (1928), in Assam, in his study of 386 ulcers, found

3 Ulcers occurred in the majority of persons with no signs or history of dietary deficiency

4 In a family when one member was affected others were rarely affected, although the same dietetic conditions prevailed

5 Ulcers were invariably limited to the lower legs Other parts of the body ought to have been affected as well if dietary deficiency was the cause

6 Healthy volunteers were successfully inoculated with the ulcer material or cultures of the fusiform bacilli

7 Ulcers in all cases responded well to treatment with copper sulfate or penicillin but not to supplementary diet

Manson Bahr reports that he has treated several severe cases in healthy and well fed Europeans Pattanayak (1944) found a number of healthy or robust persons developing tropical ulcers Pandit (1946, 1947) working in an endemic area for 3 years did not notice malnutrition in any case Roy (1928) in his study of a large number of cases in the tea gardens does not consider malnutrition to be the chief predisposing cause Bharucha (1943) had 179 patients all Indian soldiers receiving a uniform diet as laid down by Army authority, not known to be deficient in any essential constituents

It is clear from all these reports that diet calcium or vitamin deficiencies are not essential predisposing causes

Associated Diseases and Debility

Associated diseases and debility have been cited by various workers and much stress has been laid particularly on malaria and hookworm infections as possible predisposing causes Manson Bahr has pointed out that the distribution of the disease follows that of malaria Malaria however is rampant every year in the villages of Bengal in India but tropical ulcer is unknown there for years Patterson (1908), with his vast experience in Assam was convinced that malaria kala azar and debilitating conditions did not influence this disease Bharucha (1943) wrote that associated diseases such as malaria dysentery anemia and avitaminoses were not present in an active form in his 179 cases Marsh and Wilson (1945) believe that even if associated diseases are neglected the ulcers will heal with proper local treatment It is not reasonable to place the blame on the associated diseases when epidemics of the disease occur in certain seasons and treatment with penicillin cures all cases in spite of nontreatment of associated diseases Such diseases of course lower the vitality and tend to prolong the course and severity of the disease

The important causes can be summarized in the alliterative words of Marsh and Wilson (1945) all beginning with the letter "F" "Filth Food Friction and Fusospirillosis" Infection with the fusiform bacilli is the major factor as will be shown later Under the present state of our knowledge spirochetes cannot be incriminated in the etiology Lack of cleanliness is certainly a more contributory factor than friction or injury for even after implantation of the fusiform bacilli through injury if proper care is taken the disease is very likely to be prevented Lack of food that is, malnutrition, lowers the vitality and may render patients liable to infection, proof of this is not yet established however There is of course no doubt that when once a person is attacked malnutrition and debility will prolong the course and severity of the disease

serum agar, by Slanetz and Rettger (1933) on blood or potato extract agar with gentian violet under an atmosphere of 2 per cent carbon dioxide gas, by Smith (1933) on sheep serum agar with a fragment of ulcer tissue and poured plate method Most of the workers obtained, in 3 to 5 days, fine colonies like those of Streptococci, with irregular edges

Microscopically, Krumwiede and Pratt described the bacilli as slightly curved, with *tapering ends, sometimes* filamentous or in long chains, gram negative, nonmotile, and fermenting galactose and saccharose, with a foul odor in cultures Bergey describes the fusobacterium as gram negative rods with tapering ends, usually nonmotile, and showing granules in the body With Giemsa stain, the bacilli are light brown with maroon colored granules (Fox, 1921)

More recently Panja (1945) successfully cultivated the fusiform bacilli anaerobically on sheep blood agar in which he incorporated a little sterilized pus from tropical ulcers. A thick inoculum was streaked on blood agar slope or plate Fine, translucent colonies were seen after 3 to 4 days' incubation at 37° C The majority of the cultures were viable for 7 to 10 days only Solidified serum or egg medium was found liquefied when it was inoculated with pus containing fusiform bacilli Microscopically, the organism was sometimes seen to be motile, showing brisk, twisting, and sometimes a circling movement It was gram negative, fusiform, arranged either singly or in pairs or in chains characteristically clustered Seshadrinathan (1945) obtained pure cultures of the bacilli on 1 per cent nutrient agar incorporated with 25 per cent rabbit blood in an atmosphere of 90 per cent hydrogen and 10 per cent carbon dioxide at 37° C by the cup technic He put fine emulsion of pus made in normal saline into the cup and obtained transparent fine colonies a little away from the cup, but his subculture was not successful Pandit (1946, 1947) reported cultivation of the fusiform bacilli from tropical ulcer on blood agar in an atmosphere of hydrogen and 5 per cent carbon dioxide gas Colonies are fine like Streptococci

The bacillus is a strict anaerobe, gram negative, nonmotile, pleomorphic, does not ferment any ordinary serum sugars, but produces indol The organism does not grow well on Slanetz and Rettger's (1933) medium, although the fusiform bacilli from the mouth grow very well on this medium These differ in morphology and colony characteristics from the fusiform bacilli of tropical ulcer Varney (1927) classified the fusiform bacilli isolated from various sources into four types His type III is almost similar to Panja's culture, that is, gram negative, slightly curved individual bacilli or occurring in long wavy chains and huge clusters

Spirochetes—E C Smith (1930) cultivated the spirochetes on modified Wenyon's human blood saline agar under aerobic conditions in 48 hours at 37° C

A number of workers have noted fusiform bacilli changing into spirillary forms and vice versa Tunnicliff (1906) noted in the culture of fusiform bacilli filamentous and spirillary forms Sanarelli (1927) regarded spirochetes and fusiform bacilli as different forms of the same organism In fact, he was able to change one from the other and vice versa D T Smith (1932) repeatedly found fusiform bacilli changing into spirochetal forms Smith (1933) sometimes found nonmotile spirochetal forms in third day old culture of fusiform bacilli Tunnicliff (1933) noted colonies of fusiform bacilli after the fifth day of culture changing into rough forms Microscopically, such rough colonies were found to contain spiral forms of the bacilli Tunnicliff and Hammond (1934) made a careful study of the rough colonies of fusiform bacilli and came to the conclusion that the fusiform bacillus and the spirillum were different forms of the same parasite Panja (1945) found fine colonies of pure spirillary forms on repeated subculture changing into the usual colony forms of fusiform bacilli but his spirillary forms did not resemble Vincent's spirochetes Pandit (1946, 1947), on the other hand, did not obtain transformation of fusiform bacilli into spirochetal forms It is therefore not yet definitely settled whether the fusiform bacilli and spirochetes are different forms of the same parasite

Experimental Production of Tropical Ulcer

1 **With Pus**—Experimental production of ulcer in man with pus from tropical phagedenic ulcers was tried by various workers Cross (1900), P Blanchard (1914), Balli

fusiform bacilli in only 120, and in about one half the number on repeated examination Spirochetes were found in only 7 Besides, he observed gram positive diplococci in the ulcers He was inclined, therefore, to suggest that the diplococci might be the causal organisms and fusiform bacilli were secondary invaders It might be said here that not a single worker up to this day has corroborated his finding of diplococci Panja (1945) found besides fusiform bacilli organisms such as cocci, diphtheroid bacilli gram negative bacteria and sometimes Clostridia but there was no constant association between any of these organisms and active stage of the ulcer except with the fusiform bacilli

Panja (1932, 1937 1938 1943) found fusiform bacilli in all his cases and suggested that their presence was a criterion for diagnosis A fact of great importance in some of his cases was that in 17 ulcers, fusiform bacilli alone were found by him on repeated microscopic examinations and no other organisms were detected by aerobic culture using blood agar The fusiform bacilli seemed to disappear when the ulcers were healing but reappeared when healing was interfered with by artificial means A constant association was noted by him between the presence of fusiform bacilli and the characteristics of a typical phagedenic ulcer



Fig 188 —Leptothricial forms of fusiform bacilli as seen in Naga sore pus under oil immersion objective

The overwhelming evidence is that fusiform bacilli are constantly associated with tropical ulcers and spirochetes only partially These latter may either be living in symbiosis with the bacilli or may represent some stage in the development of the bacilli There are some proofs, as will be shown later on in support of this latter proposition The absence of fusiform bacilli in a few cases can be explained by the following facts that such ulcers may not be tropical ulcers at all that the ulcers may be in the healing stage when search for the bacilli is made and that a thorough search for the bacilli has not been undertaken from day to day

Fusiform bacilli have also been found often in the undermined edges of ulcers whereas none has been seen from the surface of such ulcers

Cultivation of Fusiform Bacilli and Spirochetes

Fusiform Bacilli —Fusiform bacilli are reported to have been successfully cultivated years ago under anaerobic conditions by Weaver and Tunnicliff (1905) on horse serum agar, by Tunnicliff (1906 1911 on ascitic agar slants, by Peters (1911) on Dorset's egg medium by Krumwiede and Pratt (1913) on horse serum agar by their special inverted Petri dish method of anaerobiosis by [illegible] et al. (1919), by Panja (1932) on gelatin

copious pus and typical gram negative fusiform bacilli, seen not only in films but also in pure state by culture He could not find any spirochetes or other microorganisms in any stage of the reproduced ulcer Ulcers healed in 10 to 20 days without any treatment except a sterile dressing Cultures from experimental sores yielded a pure growth of fusiform bacilli, and with subcultures from the artificial sores further tropical ulcers were reproduced Ulcers were also produced with a mixture of fusiform bacilli and Streptococci and such ulcers were larger and took a longer time to heal As he did not find spirochetes in the ulcers in any of his cases he had no occasion to try cultures of spirochetes and inoculation experiments with these Small doses of cultures of *Staphylococcus aureus Streptococcus pyogenes* diphtheroids and *Pseudomonas aeruginosa* that were isolated from some natural ulcers were injected intradermally into volunteers followed by crushing of the tissues at the site of inoculation but no typical tropical ulcer with presence of fusiform bacilli could be reproduced His key notes of success were heavy inoculum intradermal injection, repeated crushing of tissues after inoculation and application of bandage to prevent access of air and light

Vincent (1945) reproduced ulcers with cultures of fusiform bacillus in guinea pigs and rabbits by previously crushing the tissues at the site of inoculation and reproduced larger ulcers when Staphylococcus Streptococcus and Pseudomonas were mixed with the culture of fusiform bacillus He therefore came to the conclusion that the tropical ulcer was caused by fusiform bacilli frequently in association with *Borrelia vincentii* and other microorganisms especially Staphylococcus and Streptococcus Pandit (1946 1947) with great difficulty succeeded in obtaining a pure culture of the fusiform bacillus on blood agar in an atmosphere of hydrogen and 5 per cent carbon dioxide gas with a thick suspension of fresh culture he inoculated 5 volunteers intradermally but did not succeed in reproducing the ulcer His failure appears to be due to the fact that he probably did not repeatedly crush the tissues at the site of inoculation nor cover with a bandage

Serology

Panja (1945) found fusiform bacilli isolated from ulcers agglutinable with the rabbit sera against several strains of the bacilli, agglutinins were also found in some sera during recovery As the bacilli were autoagglutinable slide agglutination test with fresh cultures were carefully conducted

Summary of the Facts on Bacteriology

On reviewing all this research on the etiology of the disease a tentative conclusion can be made An infection is the major factor in the causation of the disease though Blank (1947) has raised the question as to why thousands of American troops working in the endemic area of Assam escaped the disease and why there was no infection transmitted from one person to another This can easily be explained by the fact that the fusiform bacillus is a strict anaerobe and cannot therefore multiply in an unbroken and clean skin Even if the bacillus is implanted on an injured skin it cannot produce an ulcer if care is taken of the injury at the beginning American troops know very well how to take care of their injuries That the fusiform bacillus is the true cause of the disease is established by the following evidences given by Panja (1945)

1 Fusiform bacilli are constantly associated with typical active tropical phagedenic ulcers and no other ulcers No such constant association is seen with spirochetes or any other microorganisms that are sometimes found in the ulcers

ano (1916), Shillong (1919), Fox (1921), Pampana (1923) Burnie (1931), Panja (1932, 1945), and Pandit (1946) succeeded in reproducing ulcers in human volunteers by inoculating them with the pus from tropical sores Blanchard's first attempt was unsuccessful, but in his second series of cases he succeeded by first necrotizing the skin with concentrated potassium hydroxide solution and 5 days later applying the pus on the necrotic area Apostolides (1922) records the case of a nurse whose forearm was scratched with an infected knife that had been used to incise a tropical ulcer 2 hours previously An ulcer similar to tropical ulcer developed at the site of the scratch Panja inoculated the arms and legs of volunteers intradermally with the pus and covered with a sterile dressing On the third day, a pustule formed, within 7 days, a typical ulcer showing fusiform bacilli developed In some of his cases, he performed the very important experiment of using samples of pus showing only fusiform bacilli on microscopic as well as cultural examination and succeeding in reproducing the ulcer The filtrate of such pus was found non infectious The same was corroborated by Pandit He also applied such pus on ordinary ulcers and found that typical tropical ulcer developed in a few days On the other hand, workers such as Sen (1922), Ruge et al (1925), and Smith (1933) failed to reproduce the ulcers Still, on the basis of accumulative evidences of expert workers, there is little doubt that the pus from a typical tropical ulcer showing fusiform bacilli is infectious to man and, when inoculated either on arms or legs, can reproduce typical ulcers showing the fusiform bacilli

As regards experimental reproduction of ulcers in animals, the majority of workers have failed

2 **With Cultures**—As very few workers have succeeded in obtaining a pure culture of the fusiform bacilli or spirochetes on laboratory media attempts at reproducing ulcers with cultures of the bacilli or spirochetes have not been undertaken on a large scale Fox (1921), in India, inoculated men with impure culture of fusiform bacilli, his experimental ulcers were atypical "not at all like the Naga sore," in his own words Panja (1932), in Calcutta, applied pure cultures from gelatin serum agar to scarified skin without any success, but when the culture was mixed with gram positive cocci or diphtheroid bacilli, an ulcer was reproduced but lasted for a few days only Smith (1933), in Africa, tried inoculation experiments on 8 volunteers with a pure culture of the bacilli isolated by him Boil like lesions developed in 2 cases only, typical ulcer in none, and ulcers regressed in 2 to 5 days showing only scanty fusiform bacilli

Smith (1930) believed Spironema to be the cause He reported he had succeeded in culturing the organism in modified Wenyon s blood saline agar His culture consisted of spirochetes, fusiform bacilli and *Pseudomonas aeruginosa* With this mixture he reproduced ulcers showing fusiform bacilli and spirochetes His culture was, therefore, not pure and his results were not confirmed by Brown (1935) Berry (1943) carried on an interesting observation for 3 years in the school children in Nyasaland He noted that when abrasions on the skin of the children were infected with cocci, no ulcers occurred, but when infected with cocci as well as fusiform bacilli typical ulcers were seen He also found a preponderance of fusiform bacilli on the skin during the rainy season This he supposed to be due to dampness and flies

Panja (1945), during the epidemic of 1943 in cases of tropical ulcer in Calcutta, repeated his previous finding (1932) He succeeded in obtaining pure colonies of fusiform bacilli like those of Streptococci on his "pus" blood agar medium, and later on ordinary freshly prepared sheep blood agar He inoculated 11 apparently healthy volunteers intradermally either on the upper arm or lower leg with 0 2 c c of a thick suspension of 5 different strains of pure cultures of fusiform bacilli in the third or fourth generation The site of inoculation was squeezed hard with a pair of sterilized forceps immediately after inoculation and on 2 subsequent days so as to crush the tissue and produce the required oxidation reduction potential for multiplication of the fusiform bacilli, a sterile dressing was kept on the lesion In all the cases ulcers developed, preceded by a purulent bleb and marked edema and tenderness at the sites of inoculation varying from one half to 1 inch in diameter within 4 to 6 days. Fever with rigor and edema of the whole limb were present at the beginning in some cases, but these soon subsided, leaving only an ulcer discharging

corroborate this It is interesting to make a note of a very early observation made by Young (1932) that the termite (a white ant) may be the reservoir of infection He found the ant harbored the fusiform bacilli but his observation has not been confirmed

Mode of Infection

Clements (1936) has suggested that spitting or application of saliva or chewed grass to wounds transmits the infection from the mouth Flies have been reported as probable vectors by Patterson (1908), Fox (1921) and Grenoilleau (1946) but no support is given to this mode of transmission by Roy Panja and Pandit Patterson believes that the eye gnat which has close seasonal coincidence with the ulcer may be responsible for spread of the disease Roy (1928) on the other hand carried on artificial experiments in Assam with mango flies and eye gnats (*Siphunculina funicola*) fed on tropical ulcer he concluded that such gnats were incapable of producing ulcers on scratches and could not play a prominent part in an outbreak He suggested that the prick of the shrubby herb (Mimosa), which is abundantly present in the tea gardens might carry the infection from the soil to the skin

HISTOPATHOLOGY

Histopathology has been studied in detail particularly by Keysselitz and Mayer (1909) Wolbach and Todd (1912) J C Smith (1932) Clements (1936) Panja (1945) and Pandit (1947) In the homogeneous upper layers of the

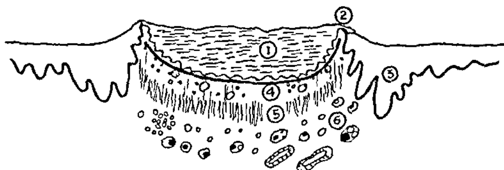


Fig 189—Naga sore diagnostic section *1* slough *2*, elevated edge *3* acanthosis in the prickle cell layer *4* vascular granulation tissue *5* felted mass of fusiform bacilli *6*, granulation tissue—plasma cells endothelial cells eosinophilic cells red blood cells—reaching up to sweat glands

ulcer composed of pus and slough pus cells red blood cells fibrin fusiform bacilli often pyogenic organisms and sometimes spirochetes are found In the deeper layers an extensive coagulation necrosis is seen in the form of a pseudomembrane Next to this that is a little below the floor of the ulcer a dense palisade' of fusiform bacilli forms a diagnostic picture Below this row of fusiform bacilli there exists a dense and very thick layer of vascular granulation tissue and polymorphonuclear leucocytes Wolbach and Todd noted also an extensive plasma cell infiltration They also found (Levaditi s

2 In some tropical ulcers fusiform bacilli only are found by microscopic and cultural examination and no other microorganisms either by microscopic or aerobic cultural examination

3 On histologic examination as will be shown later in the chapter fusiform bacilli have penetrated into the deeper layers of the ulcer while secondary invaders are found more superficially

4 The disease is reproducible in a number of human volunteers with pure primary as well as the third or fourth subculture of the organism under a special technic and the organism is recoverable in pure culture from experimental ulcers Ulcers are also reproduced with cultures of the organism isolated from experimental sores Koch s postulates are thus fulfilled

5 The disease may also be reproducible in animals if suitable precautions are taken

6 No evidences of a virus are found in the ulcer

7 Malnutrition deficiencies debility associated diseases and local infections with organisms other than the fusiform bacilli prolong the course of the disease

8 Infection as will be shown later is derived from the soil and the grasses, therefore the barefooted laborers are more commonly affected during the monsoon and postmonsoon months when they are engaged in active work

9 Infection enters through some break in the skin caused either by trauma or skin disease Poor laborers often acquire the disease because (a) they are more liable to injuries during work and (b) they do not take care of their injuries

Reservoir of Infection

Apostolides (1922) and Clements (1936) put forward evidence regarding human mouths as possible sources of fusospirochetal infection But Panja (1945) found the gums of most of his cases healthy and was not convinced of the possibility of infection from the mouth Pandit (1947) went still further and demonstrated that the mouth fusiform bacilli were different from the fusiform bacilli of tropical ulcers in their morphology colony characters and the ease with which they are cultivatable on Slanetz and Rettger s (1933) medium Roy (1928) has suggested that the soil may be the source of infection He found cases of clean ulcers without any fusiform bacilli returning with slough and fetid odor and full of fusiform bacilli when the patients were allowed to go about in the mud without any surgical dressing Panja also suspected the soil as the source of infection and went on to say that the infected soil from the endemic areas of Assam was carried during the war by the wheels of motor lorries plying incessantly from Assam to Bengal Grenoilleau (1946) is reported to have actually found the fusiform bacilli in the soil particularly when wet Napier (1947) in his book on tropical medicine states that the bacilli remain below the superficial soil in the dry season but come out on the top with the mud in the rainy season There is no doubt that the soil theory is attractive, but further experimental proofs are necessary to

Starting Point—The ulcer starts most commonly in some form of trauma—cuts, abrasions, bites, or some skin disease. Mohanty (1945) gives his figures in 76 ulcers from 36 cases thus: 29 on abrasions, 12 on blebs due to tight shoes, 6 on superficial cuts, 3 on boils, 25 on scabies, and 1 on burn.

Number—Ulcers may be single or multiple. Some authors found single ulcers in 90 per cent of their cases. Panja (1945) found single ulcers in 35 cases out of 61, and Pandit (1947) in 50 cases out of 75. Multiple ulcers may be from 2 to 20. Delsarma (1945) found 14 in 1 case. Panja found 16 in 1 case and 20 in another.



Fig 190—Ulcus tropicum 1 year

Size—The size varies from that of a pea to more than 2 inches in diameter. The majority are from 1/6 to 2½ inches (Luthra 1946 ½ inch to 3½ inches, Seshadrinathan ¼ inch to 3½ inches). The largest size recorded by Rao (1946) is 4 by 12 inches and by Luthra 5 by 10 inches.

Shape—Circular or oval, more often circular, and sometimes so nearly perfectly circular as if marked out with a compass.

Edge—Raised, undermined and bluish red. The ulcer has a cup shaped appearance. The surrounding tissue is generally normal but in early cases is edematous and red.

stain) spirochetes in the granulation tissue at a considerable depth below the surface of the ulcer Keysselitz and Mayer confirmed this finding Smith by practicing two kinds of staining—one by the Warthin method and the other by dilute Giemsa stain—demonstrated spirochetes ahead of the row of fusiform bacilli invading to a considerable depth the granulation tissue at the base He found the Malpighian layer of the epidermis in the neighborhood of the ulcer margin densely infiltrated with spirochetes Spirochetes were also observed by him in the walls of small blood vessels Costa (1944) also demonstrated spirochetes in the depth of the ulcer At the margins of the ulcer there is marked acanthosis that is an extensive proliferation of the rete It is interesting to note that Clements found the above histologic changes in his experimental ulcers also in rats

When an ulcer is in the chronic indolent stage these histologic changes are not found except for the presence of granulation tissue and newly formed fibrous tissue Golden and Padilla (1946) in their very careful and excellent histologic study demonstrated widespread damage of arterial and venous supply resulting in stenosis of lumina but unfortunately the ulcers they investigated at Guatemala were not typical phagedenic ulcers showing copious pus and fusiform bacilli

CLINICAL PICTURE

As a rule the typical clinical picture in the active stage of the disease presents itself in the form of a painful ulcer circular or oval 1 inch to 2½ inches in diameter The ulcer is full of copious and sometimes foul smelling grayish yellow blood tinged thick slough with serosanguineous discharge delimited by raised clear cut and slightly undermined margin and is commonly situated on the anterior aspects of lower legs of barefooted laboring people It is especially found during the months of July to December On microscopic examination the pus shows many gram negative fusiform bacilli and there also may be spirochetes and other microorganisms present Thus the disease is a distinct clinical and bacteriologic entity

The incubation period varies from 2 to 4 days

Site—The ulcer is commonly found below the knees that is on parts of the body most exposed to telluric contamination Lichtman (1947) found it on the anterior surface of legs in the middle or lower third in 41 4 per cent of the cases Occasionally the trunk elbows and fingers are affected and destruction of the nail bed may follow

Now the question arises as to why the lower legs and ankles are so commonly involved The answer to this is that the infection is derived from the soil and grasses that the legs are most liable to trauma particularly in the barefooted and that the adventitia of blood vessels of the lower third of the leg is very richly supplied with vasoconstrictor nonmedullated nerve fibers with the result that the amount of blood available to the tissues is reduced rendering the latter more prone to infection

larged and tender glands in only 4 per cent of his cases, and Apostolides (1922) in 10 per cent only It is only when there is a secondary infection with cocci and gram negative bacilli that glands are involved, and in such cases pyogenic organisms are found in the ulcers as well as in the glands The disease is, as a rule, nonfebrile except in very severe cases with pronounced secondary infection and complications Clements has recorded fever in the acutely phagedenic type in young children

COURSE AND PROGNOSIS

Prognosis is usually good Death is extremely rare though morbidity is high in some countries Most cases heal in 6 weeks to 3 months Average stay in the hospital before penicillin treatment was discovered was 141 days (Hughes 1931), though copper sulfate or "lock up" treatment considerably reduced the number of days On the other hand, Pinkerton (1947) from South Iran, writes that before the advent of penicillin type II acute phagedenic ulcer used to cause death unless amputation was performed

IMMUNITY

There is no immunity, either local or general A patient may get another fresh ulcer when old ulcers have completely healed Panja (1945) could reproduce fresh ulcers at the sites of healed ulcers Pandit (1945) recorded recurrence of ulcers within 1 year in 8 per cent of his cases Lichtman (1947) noted scars of previous ulcers on the backs of hands and forearms in 43 per cent of his cases

COMPLICATIONS

As a rule there are no complications and the disease is arrested at the deep fascia but sometimes bones and tendons are exposed Bharucha (1943) found osteoplastic periostitis in 13 cases out of 179 cases studied Formation of subperiosteal new bones or extensive osteoporosis was noted Shepherd (1946) observed osteomyelitis in some of her cases There is at times a serious danger to the life or limb of a patient At Uganda, 2 cases are on record a father had an ulcer which divided his tibia and the son was suffering from an ulcer extending from knee to ankle Both had to undergo lifesaving amputation Spontaneous fractures of tibia and fibula have been recorded Tetanus, erysipelas, lymphangitis, and phlebitis may occur but they are extremely rare

In a few cases, *Staphylococcus aureus* has been isolated by blood culture by some workers

DIAGNOSIS

The phagedenic phase of the disease commonly seen presents no difficulties in diagnosis The points for diagnosis are

1 Circular or oval ulcer with raised, clear cut, slightly undermined margin, cup shaped, full of copious, grayish yellow, blood tinged pus and slough with serosanguineous discharge, very tender to touch, and situated as a rule on the lower extremities, below the knees

Cavity—Cup shaped, full of grayish yellow, blood tinged, thick, often foul smelling pus and slough *Pus is sometimes so copious that several spoonfuls can be removed with a Volkmann s spoon* The pH of pus varies from 7 4 to 8 0

Floor—Formed by exquisitely tender bleeding granulation tissue The slough is adherent to the base The ulcer may exceptionally be deep enough to expose tendons muscles and even bones Lichtman (1947) records extension to tendons and bones in 34 per cent of his cases In the majority of cases the ulcerative process does not extend beyond the deep fascia

Evolution—Various stages of the ulcer have been described In the early stage there is either a bleb with seropurulent and sanguineous content or a blunt conical painful papule In 2 or 3 days the characteristic phagedenic or sloughing phase starts and by a process of coagulative necrosis pus and gangrenous slough are formed The ulcer spreads rapidly in 5 to 8 days and the patient feels difficulty in walking and sometimes has to be carried in



Fig 191—Naga sore showing typically raised margin.

arms A peculiar watery serosanguineous discharge with a putrid odor runs down from the ulcer Later after weeks or months the chronic indolent stage begins The edge of the ulcer becomes rolled and the base hard, slough is either absent or present to a slight degree fusiform bacilli are no longer found and pain is considerably diminished It is at this stage that considerable disagreement has occurred as to correct clinical bacteriologic and histologic diagnosis It may be that the so called tropical ulcers in Guatemala (Golden and Padilla 1946) are of this stage The authors have not found in ulcers of 2 weeks duration any exudate or fusiform bacilli

In the healing stage the ulcers are clean and practically painless Epithelization starts at the periphery Microscopic examination may show gram positive cocci only The healing is often slow and ends in a whitish scar

Neighboring glands as a rule are not enlarged Pattanayak (1944) and Albasi (1944) did not find any enlarged glands Clements (1936) found en

by each with his own form of treatment After prolonged suffering spontaneous cures have also been noted A careful dressing with simple normal saline alone cures many cases To assess the value of a particular form of treatment several factors such as the number of days for cure the state of health of the patient his diet whether the treatment is ambulatory or the patient is in a hospital and the stage of the ulcer—all should be taken into consideration

Hare (1946) has summarized the comparative value of several lines of treatment as follows

Bharucha (1943)—Dressing with copper sulfate solution 1 in 150 until all sloughs separate then dressing with 40 per cent codliver oil in petroleum jelly average healing time 35 to 54 days but dressing with sulfanilamide and iodoform powder each 50 per cent average healing time 20 to 36 days

Panja and Ghosh (1944)—Dressing with sulfanilamide dusting powder average healing time 21 to 42 days but sulfanilamide dusting powder locally in the early stage and copper sulfate in later stage average healing time 40 days

Rao et al (1945)—Sulfathiazole paste (sulfathiazole 12 calcium oleate 2 beeswax 3 codliver oil 60 water 40), average healing time 30 to 35 days

Marsh and Wilson (1945)—Occlusion by plaster of Paris after bipp and zipp * average healing time 31 to 39 days

Brecher (1946)—Occlusive treatment by adhesive plaster average healing time 42 days

Hare (1946)—Vitamin A by mouth and dressing with codliver oil average healing time 45 days but dressing with zipp average healing time 39 days

James (1932)—Excision and skin grafting average healing time less than 2 weeks very successful

Numerous drugs have been used by various workers

Bactericides Formalin iodine mercury iodoform electrolytic chlorine eusol

Spirocheticides arsenic bismuth antimony

Oxidizing agent potassium permanganate

Reducing agent pyrogallic acid

Caustics copper sulfate silver nitrate phenol

Dyes acriflavine Mercurochrome gentian violet

Astringents

Emollients

Hydrotherapy

A resume of the treatment by various workers is given

Vincent s Dusting Powder—Vincent (1945) dried the ulcer after cleaning with normal saline and then applied the dusting powder (calcium hypochlorite 1 part boric acid 9 parts) and renewed the dressing every 3 or 4 days He noticed healing in 2 or 3 weeks Corpus (1924) more than 26 years ago followed practically the same method He washed with a solution of potassium per

*Zipp — zinc oxide 1 iodoform 2 and liquid paraffin 2

2 Patients are often barefooted laborers usually from an generally poorly nourished

3 History of trauma or skin lesion frequently present

4 No constitutional symptoms as a rule

5 The criterion of diagnosis the presence of fusiform times of spirochetes

DIFFERENTIAL DIAGNOSIS

The following diseases come under consideration in differe

Veld sore (Septic sore desert sore Barcoo rot) is a punched-out ulcer usually multiple present on the back of t arms or legs and sometimes on the face mainly seen in Eur in the tropics The ulcer begins like the vesicle of an impetig colored fluid There is little undermining under the edge Str Staphylococcus only are usually found in the discharge

Cutaneous diphtheritic ulcer is a punched out deep ulcer per cent of cases with rolled edge and floor covered by adher seen usually in Europeans and located on their extremities

Corynebacterium diphtheriae can be isolated in the majori Faucial diphtheria occurs in some of the cases and diphtheria isolated from the nose and the throat Diphtheritic neuritis as a complication Antidiphtheritic serum 4 000 units subcut vicinity of the ulcer shows a strikingly beneficial effect

Diphtheritic ulcers of Chittagong hill tracts of India (Garig sore) are found on the lower extremities have rolled edges covered by membrane and little or no pus A virulent diphthe been isolated from every case and ulcers have been reproduced of the bacilli (Pasricha and Panja 1940) Antidiphtheritic value in such ulcers

Cutaneous leishmaniasis (Oriental sore Baghdad boil or seen on exposed parts of the body it starts with a hard papule later into an ulcer with ragged edges thick crust on the top a dish edema at the periphery *Leishmania tropica* is easily demo scrapings of the ulcer or at the edematous margin

Ecthyma is a superficial stubby ulcer with a hard edge an lowish crust and without any undermining Staphylococcus Streptococcus are found in the lesion sulfathiazole therapy s cific

Syphilitic gummatous ulcer yaws varicose ulcer, trophic u tuberculous ulcer, cancerous ulcer, sporotrichosis and **indole** various causes must sometimes be distinguished from the trop ulcer There are no fusiform bacilli in any of these lesions

TREATMENT

Papers have been published on this aspect of the disease m

Connell and Buchanan (1933) used with success zipp (zinc oxide 1 iodc form 2, and liquid paraffin 2) first and then applied plaster of Paris on th top Grindlay (1944) recommended dusting with a sulfonamide after me chanical cleaning, then application of zipp with a piece of lint and on th top plaster of Paris kept in position for 2 to 3 weeks After this period h found clean granulation tissue ready for skin grafting Connell (1944) als advocated exactly the same method Walker Taylor (1945) practiced curet tage or excision followed by occlusive dressing with plaster of Paris and h found the average number of days of hospital stay to be 28 2 in the first grou of cases and 17 8 in the next group Diniz (1945) also used plaster of Paris but called the method "Zeno process" which was recommended for burns b Professor Zeno in 1943 Hammond (1945) used with success the occlusiv dressing made up with plaster of Paris 3 tragacanth 1 and acriflavine 0 001 all ground in a mortar before application He called such a dressing "Almaz Patch" Marsh and Wilson (1945) advised their "lock up" method of treat ment by bipp followed by zipp and then encasing the lesion in plaster o Paris Out of 81 cases 59 healed in an average time of a little over 2 weeks Gill (1945), in Palestine practiced the ambulatory treatment with satisfac tory results by dusting first with sulfanilamide powder and then applying plaster of Paris The ulcers healed in 1 to 3 weeks Jarvis (1945) used zipp followed by plaster of Paris with apparently good results

Adhesive plasters were used by some workers in place of plaster of Paris Sayers (1932) reported excellent results with a 3 inch spiral bandage of ad hesive elastoplast changed every 3 to 4 days and later weekly Bell (1934) used strapping with adhesive zinc oxide plaster with gratifying results Nath (1946) recommended strapping with Leucoplast in place of plaster of Paris and noticed healing in 15 days whereas treatment with copper sulfate and sulfonamide resulted in healing in 35 days a much longer time than in the fixation method

Local Sulfonamide Therapy—Bayley (1939) reported good results with sulfanilamide applied externally Earle (1942) used sulfanilamide locally in early ulcers and found local application of whale oil extremely valuable in advanced ulcers Abbasi (1944) recorded "marvelous results" in his 11 cases with sulfanilamide dusting powder Mina (1945) painted the ulcers with 2 5 per cent tincture of iodine and then covered them with a dry powder con sisting of sulfanilamide 1 part and magnesium sulfate 1 part Healing took place in 8 to 14 days He deprecated the use of watery solutions of any anti septic Scovel (1946) used daily dressing with sulfonamides and zinc perox ide for 5 days followed by daily irrigation with warm normal saline under moist dressing for 8 days Finally, he practiced surgical method of treatment by pinch skin grafts Hare (1946) made a comparative study of the treat ment by sulfonamides copper sulfate magnesium sulfate, and codliver oil but finally decided on penicillin as the best In his large series of cases Grenoilleau (1946) used sulfanilamide dusting powder, he sprayed Sulfarsenol or Novoarsenobenzol solution every 2 to 3 days and achieved rapidly a good

manganate (1 4 000) and then dusted with Vincent s powder and found clean granulation tissue from the fourth to sixth day

Copper Sulfate—Treatment with local application of copper sulfate was first advocated by Annesley (1828) in the Burma expedition more than a century ago and later in 1922 by Mathur who reported that all the ulcers healed quickly when treated with copper sulfate lotion He went on to say that the drug appeared to be specific Still later, in 1925, the drug was used by Terdschanian in 10 per cent strength McGuire (1933) used the drug in the following formula copper sulfate *180 gr phenol pure 1 fluid drachm* distilled water 1 fluid ounce this formula was followed by a dusting powder composed of iodoform 1 part and bismuth subgallate 3 parts and was used for 2 years in about 2 000 cases in the Assam tea gardens McGuire found it extremely useful One objection to the use of this mixture is that phenol is not soluble in the small amount of water used and therefore it floats on the top of the water Later (1944) he followed James (1938) and replaced water by glycerin Gunther (1938) used the drug in a dilution of 1 150 as a wet dressing renewed it every 4 hours and continued in this way for 36 hours when all sloughs cleared up *He found the drug to be apparently specific James (1938) advocated the formula copper sulfate 240 gr phenol 1 fluid* drachm glycerin 1 fluid ounce The results were good Such an application according to Panja (1945) was too strong and caused much pain sometimes lasting for the whole night and disturbing sleep Earle (1940) used the drug successfully in the same strength as Gunther Panja and Ghosh (1944) employed the drug at the beginning to remove all sloughs and then recommended dusting with a sulfanilamide powder Panja (1945) advised repeated dressing at least 3 times a day by irrigation with plain boiled water or weak mercuric chloride solution to remove the anaerobic condition formed by the thick slough and under which the fusiform bacillus shelters and multiplies The irrigation was followed by painting with copper sulfate solution in glycerin (copper sulfate 120 gr phenol 1 fluid drachm glycerin 1 fluid ounce) and was then repeated soon after the pain so as to remove the excess of the caustic Finally to ensure anaerobiosis a thick absorbent pad soaked in a solution of potassium permanganate (1 5 000) was applied All pus and sloughs from even bad cases disappeared in 2 to 4 days When no pus was noticed for 3 to 4 consecutive days and when clean granulation was visible it was only then that the use of copper sulfate was discontinued and plain boric or scarlet red ointment was applied To test the real efficacy of a drug Panja waited for the result after applying a final dressing with a bland ointment and not with saline because a saline dressing alone repeatedly changed was found by him to cure several cases Smythe (1946) treated 627 cases by first washing and then painting with pure phenol instead of copper sulfate solution 6 times a day he found the result satisfactory

Occlusive Dressing—Occlusive dressing by plaster of Paris has been advocated by a number of workers Connell and Buchanan (1933) Grindlay (1944) Connell (1944) Walker Taylor (1945) Irvine (1945) Diniz (1945) Hammond (1945) Marsh and Wilson (1945) Gill (1945) and Jarvis (1945)

Connell and Buchanan (1933) used with success zipp (zinc oxide 1 iodoform 2 and liquid paraffin 2) first and then applied plaster of Paris on the top Grindlay (1944) recommended dusting with a sulfonamide after mechanical cleaning then application of zipp with a piece of lint and on the top plaster of Paris kept in position for 2 to 3 weeks After this period he found clean granulation tissue ready for skin grafting Connell (1944) also advocated exactly the same method Walker Taylor (1945) practiced curettage or excision followed by occlusive dressing with plaster of Paris and he found the average number of days of hospital stay to be 28 2 in the first group of cases and 17 8 in the next group Diniz (1945) also used plaster of Paris but called the method Zeno process ' which was recommended for burns by Professor Zeno in 1943 Hammond (1945) used with success the occlusive dressing made up with plaster of Paris 3 tragacanth 1 and acriflavine 0 001 all ground in a mortar before application He called such a dressing Almazi Patch Marsh and Wilson (1945) advised their lock up ' method of treatment by bipp followed by zipp and then encasing the lesion in plaster of Paris Out of 85 cases 59 healed in an average time of a little over 2 weeks Gill (1945) in Palestine practiced the ambulatory treatment with satisfactory results by dusting first with sulfanilamide powder and then applying plaster of Paris The ulcers healed in 1 to 3 weeks Jarvis (1945) used zipp followed by plaster of Paris with apparently good results

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effect Smythe (1946), on the other hand found sulfonamides or iodoform of little value in the active stage of the disease

Iodoform—Kerby (1932) obtained best results by curettage followed by application of bipp McGuire (1933) used iodoform as a dusting powder mixed with bismuth subgallate following the treatment with copper sulfate Hoffman's (1941) zisp (zinc peroxide iodoform sulfanilamide and liquid paraffin) has also been used with success Costa (1944) cleaned the ulcers with a solution of potassium permanganate (1 8 000) and then applied 15 per cent iodoform in ether

Operative Treatment—James (1932) practiced excision and immediate skin grafting under spinal anesthesia He noted complete success in 41 out of 45 cases Healing took place in an average period of 13 days Kerby (1932) also advocated preliminary curettage to obtain the best results Skin grafting has been recommended by many workers when the ulcers are found clean and granulating

Miscellaneous—Hayman (1914) tried x ray exposure and obtained disappearance of all pain in the first few days and rapid cure by cicatrization but Clements (1936) discredits this result Corpus (1924) used 3 per cent solution of arsphenamine locally in 598 cases in the Philippines and cured 410 cases He declared the treatment most effective " James (1925) applied wet dressing with 25 per cent solution of magnesium sulfate and found it ' uniformly successful " Hughes (1931) used quinine or cinchona as a dusting powder and found very good results ' Innes (1931) like Hughes used quinine externally and recorded the results as magical Brown (1935) found magnesium sulfate as the most suitable dressing Mohiuddin (1943) used a wet dressing with Novoarsenobenzol 0 3 Gm in 1 ounce of distilled water with satisfactory result Pampana (1923) obtained excellent results with daily dressing of acriflavine solution (1 1 000) Shircore (1944) irrigated the ulcers with potassium permanganate (1 4 000) dusted with his A K powder (acriflavine 3 5 gr water ½ pint and kaolin ½ pound) and then covered with a piece of lint wrung out in sterilized almond oil every other day He found highly gratifying results Amaral in Brazil found local application of normal dried serum exceedingly successful

Summarizing all the above lines of external treatment that have been advocated and practiced in the old days the following four methods appear to be most successful (1) frequent cleansing with potassium permanganate solution (1 5 000) and dressing with normal saline (2) application of copper sulfate phenol glycerin, (3) occlusive dressing with plaster of Paris or elastoplast and (d) excision and immediate skin grafting in suitable cases

Internal Treatment

Scott (1917) found antimony parenterally useful Mei (1920) used tartar emetic intravenously and externally as a dusting powder with apparently good results Crichlow (1920) found Galyl injection ' wonderfully effective " Apostolides (1922) recorded best results with intravenous Novoarsenobenzol Abraham (1923) found good results with his new treatment namely hot

dressing with calx chlorinata and 2 per cent antimony tartrate intravenously Loewenthal (1932) gave daily intravenous injection of 15 gr of calcium chloride dissolved in 10 c c of distilled water and found rapid separation of *slough and healing* But his cure rate was 52 per cent only There was no improvement in about 12 per cent of his cases and 4 4 per cent of the patients died Brown (1935) found calcium chloride 15 to 30 gr intravenously daily definitely beneficial and also parathyroid by mouth which promoted rapid epithelization Berry (1943) used intravenous tartar emetic 1 to 10 c c of 1 per cent solution *in Indo China he reported good results Ulcers took* 6 to 8 days to heal Tournier recorded a single subcutaneous injection of 0 30 Gm of Novoarsenobenzol dissolved in 4 per cent sodium chloride most satis factory Houssiau gave intramuscular injection of bismuth on 3 successive days he also applied bismuth hydroxide externally and obtained complete healing in a case Pons found that a course of 4 to 5 injections only of anti spirillary vaccine exerted a rapid action on the ulcers and he noted cessation of all pains in 48 hours and cicatrization after the fourth day On the other hand *Panja (1945) obtained no good results with a vaccine made from cul* tures of fusiform bacilli

Conclusion

Regarding the internal treatment and general management most work ers are of the opinion that calcium arsenic antimony sulfonamides non specific vaccines or even vaccines made from a culture of fusiform bacillus and vitamin feeding are generally of no value No rapid healing or healing at all is obtained by these medicaments Rest is certainly important A deeply ulcerated locomotive organ is not expected to do well if it is burdened with gravitational stasis and at the same time allowed to continue its work *Athough ambulatory treatment may cure all cases still if rest be enforced* cure is certainly hastened If a patient is poorly nourished and debilitated or suffering from diseases such as malaria dysentery etc good feeding and treatment of his associated ailments will promote more rapid healing

PENICILLIN

Recently penicillin has been spoken of highly and declared to be the drug of choice *or apparently specific by several workers starting from Hamm* and Ouary (1944) and Panja (1945) working independently in America and India respectively down to Moreau and Ouary (1945) Blank (1947) Webb (1946) Hare (1946) Whitestone (1947) Pinkerton (1947) and Gutch (1947) Panja while working on the sores in Calcutta in 1943 had sufficient experimental and circumstantial grounds to formulate no fusiform no Naga sore and know ing that *penicillin was effective in fusospirochetal affections* he thought of trying the drug in tropical ulcer unfortunately no penicillin was then avail able to the civil population in India He had to write to Fleming for supply of a culture of *Penicillium notatum* and to prepare crude penicillin in Czapek Dox medium in his laboratory But when his crude penicillin was ready he received a supply of penicillin (Lilly) which he used externally as a dressing

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by using this method it may not be possible to have a clean base at one sitting After washing the ulcer all fluids should be mopped up with a piece of absorbent cotton wool and then a sterile pad of gauze or absorbent cotton soaked in penicillin solution 500 to 1 000 units per c c should be applied On the top of this should be put oil silk and nonabsorbent cotton and bandage The ulcer should be dressed in this way twice a day An intramuscular injection of 20 000 units of penicillin should also be given and repeated every 3 hours if the ulcer is of severe type As a rule repeated dressing with penicillin alone suffices and injections are not required When no pus is seen for 3 consecutive days a boric ointment with shark or codliver oil (2 fluid drachms to an ounce) or scarlet red ointment should be applied If there is delay in healing skin grafting by the pinch method should be practiced General condition of the patient and associated ailments should also be looked after at the same time to promote faster healing

PROPHYLAXIS

As an injury is the starting point in most cases the wearing of puttees has been advised and incidence of the disease found enormously decreased (Roy 1928) Such a practice is not always possible Cleaning of the lower legs after a day s work is very important and whenever there is any injury or impetigo or boil or bite penicillin ointment should be applied if possible If this is not available the parts should be painted with tincture of iodine followed by tincture of benzoin compound or a boric ointment may be applied Grenoilleau (1946) has advised the use of tincture of Mercurochrome and immediate bandaging In fact every precaution should be taken to prevent any skin lesion from turning into the tropical ulcer A daily routine inspection of the legs of all laborers before joining the day s work should be carried on during an epidemic season Such a procedure is sure to curtail the incidence to a very large extent Destruction of flies has been advised but this does not appear to be essential nor is it a practical proposal

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in 1 available case only in 1944 as the epidemic had then largely subsided Judging from his experiences in treating a large number of cases by various methods of treatment he was impressed with the dramatic result in 1 case alone So a note was sent in 1944 to the *Indian Medical Gazette* without any knowledge that in the same year (1944) Hamm and Ouary had found penicillin effective in 18 cases They used the drug locally in a strength of 2 800 units per c c and they found all sloughs and pain disappearing within a few days and complete healing taking place in 3 to 4 weeks Moreau and Ouary later (1945) used penicillin 250 units per c c in 19 cases as a local dressing with success Blank (1947) recorded in detail with photographs the successful use of *penicillin parenterally 20 000 units intramuscularly* every 3 hours covering 18 doses for about $2\frac{1}{4}$ days on only 1 bad case and remarked that the penicillin treatment was the treatment of choice Webb (1946) used the drug 500 units per c c as a local dressing twice a day and at the same time gave a maximum number of 6 intramuscular injections 15 000 units at a time at intervals of 3 hours Ulcers became clean in 1 to 3 days Hare (1946) practiced the combined method that is locally 500 units per c c for about 5 days and 15 000 units intramuscularly in 12 hours When the ulcers cleaned up a scarlet red ointment was applied Complete healing took place in a little over 3 weeks whereas in cases of ulcers treated by methods other than penicillin complete healing took place in more than 4 weeks Whitestone (1947) treated cases in the hospital with a local dressing of the drug 500 units per c c in most cases and also parenterally once a day but in bad cases only Average stay in the hospital was 23 1 days with the penicillin treated cases and 34 2 days in the control group of cases Pinkerton (1947) in South Iran used 2 000 units every 4 hours for 5 days and found the drug to exert a specific and rapid action He remarked also that the disease of type II that is the acute phagedenic type used to cause death before the advent of penicillin unless timely amputation was performed Gutch (1947) sprinkled dry penicillin powder over the surface of ulcers and then covered with petroleum jelly gauze In 32 cases out of 35 so treated healthy granulation tissue appeared in 1 to 3 days and he could apply pinch graft on the tenth day

From all these reports it is evident that penicillin promises to be the drug of choice for successful treatment of a disease which has hitherto incapacitated so many people in the tropical and subtropical countries of the world The advantages of penicillin treatment are that the treatment can be ambulatory there is no local or systemic reaction pain is relieved in 24 hours and quick healing takes place The treatment is also very simple and can be carried out by the patient himself

The treatment of tropical phagedenic ulcer may thus be summarized If the patient can be admitted to a hospital well and good If not he can have ambulatory treatment The ulcer should be washed thoroughly by means of a douche jet with plain boiled water or with potassium permanganate solution (1 5 000) and while the douche jet is playing on the ulcer, all adherent slough should be disengaged with a sterile cotton swab It is not usually possible to remove all the sloughs if an irrigator and a cotton swab are not used Even

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tion Also, according to Snijders, bacteriophage may be present, even in young cultures these inhibit the growth and isolation of the Klebsiella At any rate, these very rare negative results do not invalidate the thesis that this microorganism is the cause of the disease

Apart from patients, *K rhinoscleromatis* is found in a small number of persons without clinical symptoms of scleroma, living in close contact with the patients, very probably these persons must be considered as carriers of the bacterium, especially those in whom the complement fixation test has been found to be negative

The bacterium has never been found outside the foci of scleroma This also adds to the probability that von Frisch's Klebsiella is indeed the causal agent of this disease

Some authors still doubt the etiologic role of the Klebsiella Ash and Spitz (1945) and Reyes (1946), who think it probable that the disease is caused by a virus, the Klebsiella growing symbiotically in the pathologic tissue The peculiar geographical distribution of *K rhinoscleromatis*—namely, only in certain localities where scleroma occurs, and there only in patients and in some of their immediate contacts—speaks against this hypothesis

The third postulate of Koch, the empirical production of the disease by inoculation of the Klebsiella, is the only one which has not yet been realized Although this must leave some uncertainty as to the etiology of the disease, very little doubt can exist that the bacterium of von Frisch is, indeed, the causative agent of the disease The same situation exists in leprosy, in that disease the significance of Hansen's bacterium is generally accepted

EXPERIMENTAL PRODUCTION OF SCLEROMA

De Simoni (cited by Hajek) tried to produce scleroma in man by injecting an emulsion of Klebsiellae into the nasal mucosa of a cachetic tuberculous patient, without success Rona (1899) injected the bacteria into the ear lobe of a patient with nasal scleroma but here also no result was seen in the course of five months Schlotter (cited by Hajek) implanted fresh scleromatous tissue under the skin of his arm, again without result

Many authors have tried to produce scleroma by inoculating animals with *K rhinoscleromatis* Many times granulomata have actually been produced after injection of the bacteria into the skin or the eye of mice, guinea pigs rats and rabbits These lesions showed the characteristic pathologic picture of the scleroma and from these granulomata the Klebsiella could be recovered (Sercer, 1932) It is doubtful, however, whether these lesions can be considered truly scleromatous The lesion produced is a disease of very short duration The granuloma appears after 8 or 10 days, and disappears after a few weeks, so that the very important characteristic of scleroma, the chronicity, is absent

EPIDEMIOLOGY

Since scleroma was first diagnosed by Hebra, knowledge about this disease has steadily increased and with increasing knowledge more and more cases have been discovered In Russia, for instance, only 21 cases were registered in 1888, in 1911, 128 cases, and in 1932, no less than 1,400 The disease has also been described for many years in other countries

The principal focus of the disease is in *eastern Europe* the Ukraine (along the Pripyat River), White Russia, and Poland More than 75 per cent of all cases observed have originated from these countries From this large focus it spreads toward the north

CHAPTER 34

RESPIRATORY SCLEROMA (RHINOSCLEROMA)

WILLEM KOUWENAAR

Rhinoscleroma is an infectious disease of the respiratory tract, with formation of granulomatous tissue with characteristic pathologic structure, occurring from the nose to the bronchi, and caused very probably by infection with *Klebsiella rhinoscleromatis* von Frisch

It was first described by Hebra (Vienna) in 1870 in eastern Europe, and has since been found in many other countries

In the majority of the endemic foci the malformation of the nose is not the principal or clinically most important localization of the scleromatous process, in many cases this organ is not involved in the process at all It is, therefore, advisable to change the old name, rhinoscleroma, given by Hebra, and to speak of the disease as "scleroma respiratorium" or "respiratory scleroma"

ETIOLOGY

Although experimental reproduction of the disease by inoculation with *K rhinoscleromatis* has not as yet been successful, sufficient proof exists that this microorganism is indeed the cause of the disease

This bacterium, first isolated and described by von Frisch in 1882, belongs to the group of gram negative encapsulated bacteria It grows well on common media, so that it can be easily cultivated It is closely related to other capsulated bacteria, *K ozenae* and *K pneumoniae*, but cultural differences exist, and although the capsular antigens of the three species are affiliated, all examined strains of *K rhinoscleromatis* have in common a specific body antigen Thus this bacterium can be differentiated clearly from the other Klebsiellae

The *K rhinoscleromatis* proved to be a sharply defined species, strictly uniform, culturally as well as antigenically, the capsules being constantly of the "C" type The strains obtained with the necessary precautions from the patients with scleroma belonged without exception to this species and *K rhinoscleromatis* was found only in patients and their immediate contacts, and never in regions free from scleroma There exist, however, strains of *K ozenae* the body antigen of which shows close relationship to that of *K rhinoscleromatis* (Wielenga, 1937)

the scleromatous tissue and not from the surface of the mucosa With this precaution, pure cultures are as a rule obtained In slides made from the tissue, the bacterium can be found in cells which are highly characteristic of the pathologic picture of the disease, the cells of Mikulicz, and between the cells, often in a group The Klebsiellae can be cultivated in a large majority of the cases They have not been found in all patients, but negative results can be explained by the fact that material was taken from an unfavorable place, or that the bacteria disappeared as a result of local cicatrization and cessation of the process of inflamma

counteract the spread of scleroma among the population of this island. Finally in Flores, 5 cases were seen by Haulussy and Sardjito (1939)

Up to 1940, some 150 to 200 cases were found in Indonesia, so that *this archipelago* may be rightly considered as one of the major endemic centers Recalling that in most of the places systematic examination of the often backward population has not yet been carried out efficiently, the real number of infected persons may be much higher

Shawket al Zahawi saw a patient with scleroma in Iraq Some cases have also been described in Palestine, possibly imported from Russia

Possibly 1 case in a Frenchman originated in the Philippines (Argaud and Laval, 1925), however, the patient had left the islands 25 years before the disease was discovered. Crawford and Gerundo (1947) described 2 cases from Hawaii

In Central America scleroma respiratorium has been described from many countries

San Salvador Alvarez (1885), 30 cases (cited by de Moor, 1929), Reyes (1946), 200 cases

Guatemala Castellani (1926), 6 cases

Costa Rica Pena Chavarria and Nauck (1929), *5 cases in 4 years*, Rotter and Peña Chavarria (1933), 4 patients, 1 with a secondary growth in the colon, Muhlens (1927), several cases

Colombia Findler (cited by de Moor), 1 case, Peña Chavarria and Nauck (1929), according to whom the disease is located in the cooler climate of the hills

Cuba Castello Dominguez (1923), 1 case, Gonzalez (cited by Wielenga), 1 case

Martinique Vildrain (cited by Belinoff), 2 unconfirmed cases

Mexico Pietro (cited by de Moor), 1 case, Alderson (1914), 1 patient, Lewis (cited by Belinoff), 2 cases

In *Africa* the disease occurs principally in the northern part of the continent In *Egypt*, a major focus exists, as described by Cole Mallon (1929) and Shaheen Hassan Bey (cited by Wielenga), according to whom about 20 patients with scleroma are observed annually in the Cairo hospitals Some cases are described from *Morocco, Algeria,* and *Tunisia (Brault et al, cited by Argaud, Dekester and Martin, 1923, Decrop et al, 1925,* cited by de Moor, Berge 1942) In Central Africa 1 case was reported by Fischer (1932) near *Lake Victoria*, Worms (cited by Belinoff) saw 3 unconfirmed cases in *Togo*

Altogether, about 3,000 to 4,000 cases are known in the entire world, but no doubt more cases will be found The disease is by no means just a curiosity, on the contrary, it is of sufficient importance to justify more extensive examination of the population of many of the aforementioned countries as well as the surrounding districts Apart from the clinical observation bacteriologic, serologic and pathologic examination are necessary to guarantee reliable results

The distribution of scleroma respiratorium in circumscribed foci suggests *that it is a contagious disease, this hypothesis* also best explains the other epidemiologic features

Scleroma is a disease that principally attacks the poorer population According to Belinoff's vast statistics (1932), 94 5 per cent of the known cases in eastern Europe are poor laborers and peasants *The same is true of most* of the cases in the tropics Bad housing, insufficient food according to some authors (Lewis cited by Belinoff) even nutritional imbalance, and often very primitive living conditions (sleeping closely together in badly ventilated houses may be of great importance) are present in all major foci *It is es*sentially a disease of the "great unwashed" Long existing, prolonged contact in an unhygienic environment, among people of primitive hygienic hab

(Estonia, Latvia, former East Prussia), the east (Russia), the south (Yugoslavia, Hungary), Romania), and the west (Czechoslovakia, Germany) It is chiefly a disease of the Slavs, possibly they introduced it in other countries by immigration

In other European countries small foci are described, often including only a few cases *The largest foci, probably related, are found in southern Switzerland (canton of Valais) and Italy* (from the north, where most of the cases occur, to Naples and even Catania) It is possible that this focus also originates in emigration from eastern Europe Isolated cases have been described from Sweden, Denmark, and France, very probably imported

Some patients are reported in *Siberia* and *Turkestan*, most of them having migrated from Russia One case was seen in the Hopeh province in *China*

In the *United States*, several cases have been reported, the large majority imported from eastern Europe But apart from these, a number of cases have been seen in persons born in the United States and who had never left the country In statistics from the American Subcommittee on Rhinoscleroma, published by Belinoff (1932), of 37 cases registered, 26 certainly were Russians, Poles, etc, and 11 were born in North America—cases are mentioned from North Carolina and Cincinnati, Ohio (Alloway), New York (Tarell), Michigan (Howland), Greenville (Jervay), and Arkansas (Moore) Probably autochthonous cases were also described by Wende (1896, cited by de Moor), Stelwagon (1913), Watkins (1921, a Negro from Maryland, who for short times had been in South America), Kernan (1924), Canfield (cited by Wielenga, a case from Michigan, the parents had emigrated from Poland), Wood (1925, cited by Wielenga, the parents were immigrants from Austria), Figi and Thompson (1928, from New Jersey), Simpson and Ellis (1939, a patient from South Carolina), and perhaps a few others According to Cunning and Du Pont (1943), 102 cases have been reported from the United States and Canada, including 16 in native born subjects Very little is known about the contact of those patients with immigrants from a focus of scleroma in Europe or Central and South America The significance of scleroma respiratorium for the United States seems not yet clearly established

In South America, cases have been reported from *Brazil* (Florence, 1909—1 patient, Duarte, 1923—2 cases, Terra cited by de Moor—8 Negroes, Falçao, 1945, who states that 26 cases have been reported since 1890, 16 of them autochthonous), and especially from *Chile*, where del Rio (1909, cited by de Moor) saw 31 cases Scleroma has also been reported from *Argentina* (Bilina and Aberastury, 1933, who saw 5 patients from the Andes 4 born in Argentina, these cases are perhaps related to the focus in Chile) Vidal (1891, cited by Argand and Laval saw the disease in *Peru*

Endemic foci of scleroma likewise exist in *tropical countries*

In *Asia*, a relatively large number of cases have been reported from India and Indonesia In *India*, the disease is widely scattered over the northern and central parts of the country, Keegan (cited by Snijders, 1931) saw 11 cases from the Central Provinces, Castellani and Chalmers mention one case from Ceylon Acton (cited by Snijders, 1931) saw several cases from the Punjab, Nepal, Bengal, Bihar, Orissa, and the Central Provinces, Rao and Menon (1941) described 6 patients in Vizagapatam (Orissa), Mohanty (1945) one case in Orissa, Ghosh and Panja (1945) a case in Calcutta It appears that some concentration of the cases occurs on and around the Chota Nagpur plateau

In the *Indonesian archipelago*, a major focus exists After Snijders and Stoll (1921) had discovered the first patient in 1918, altogether about 90 cases were found among the Batak population in northern Sumatra (Kouwenaar et al, 1934) In southern Sumatra a focus exists in the Pasoemah district (Kuilman et al, 1937. 10 cases) In Bali, 13 patients were described by Noosten et al (1934), later 29 more cases were discovered In northern *Celebes*, scleroma is also rather frequent, Leimena and Sardito (1936) and Oomen and Kirschner (1938) found at least 15 patients suffering from the disease In *Java* several patients with scleroma were described (Djochana et al, 1934, Kuilman, 1938 a Chinese with symptoms of nose, pharynx, and larynx, Maasland, 1935, Ramali, 1936, and others) Here the cases are disseminated over the central and eastern parts of the island, and no definite focus could be found, although possibly a concentration *occurs in southeastern* Java, where more primitive conditions still prevail, Islam with its ritual ablutions will

why the disease, endemic among the Bataks of north Sumatra, never attacked the surrounding populations as the people are Mohammedans and consequently live as a rule in better conditions of cleanliness No racial immunity exists isolated cases may occur in other people but the way of living seems to be the principal factor

Probably this also explains the fact that in most of the endemic areas outside eastern Europe only small foci are found, between which no close contact exists These foci may be the remnants of a larger and more general endemic

The epidemiologic distribution *of scleroma in eastern Europe can be explained by* direct contact The connection between the scattered foci in the tropics is more difficult to understand The situation existing in Indonesia makes a hypothesis possible

At the present time a direct connection between the different Indonesian foci does not exist, but in every major focus (except possibly north Celebes) the principal inhabitants are descended from archaic strata of the population, who many centuries ago migrated in large numbers from India and are still anthropologically and ethnologically related (a common megalithic culture is found in these countries) to the Munda races from India (Chota Nagpur), among whom scleroma also occurs Possibly, as Snijders (1931) suggests, the disease was introduced in Indonesia with these migrating peoples in the remote past and has since survived among the descendants of these immigrants who still adhere to many of their archaic and primitive customs In this way, a relationship between the foci in north and south Sumatra Java, Bali, and Flores can be established

All arguments point to the belief that scleroma respiratorium is an old disease, slowly disappearing with the advent of better hygienic living conditions That the medical history of scleroma is only about 80 years old an argument used by Streit (193-) for his hypothesis that scleroma is a recent disease, can be explained by the scanty medical supervision in these usually backward countries, and by the supposition that the diagnosis formerly was faulty, just as today the uninformed make a diagnosis of leprosy, frambesia lupus or lues in classical cases of scleroma

PATHOLOGY

The scleromatous process consists principally of a massive and dense infiltration of plasma cells with some leucocytes and lymphocytes In the early stage of development many engorged blood vessels are present In the slides stained with hematoxylin eosin, many round red bodies are seen between the cells They occur sometimes in a cell with a still recognizable nucleus, sometimes the nuclei are separated after degeneration of the rest of the cell and form the bodies of Russell or Pellizari These are not specific but are found in many plasmocytic infiltrations Scattered through the infiltration single or in clusters, occur large cells with a frothy aspect usually consisting only of a small pyknotic nucleus narrow strands of cytoplasm and a membrane so that at first sight these cells give the impression of empty *holes in the preparation The cells do not contain fat* These are the cells of Mikulicz and are highly characteristic for the scleromatous process Their origin is uncertain

Except in the most recently developed parts of the granuloma *fibroblasts* may be seen, many bands of collagen connective tissue are spread through the lesion and often a hyaline mass is seen in the large parts of plasmocytic infiltration This explains the characteristic cartilaginous consistency of the scleromatous granuloma Later the connective tissue increases and in old lesions it forms the greater part of the granuloma which becomes smaller in this final stage of retraction and cicatrization

its, seems to be necessary for successful infection In this and other aspects the epidemiology of scleroma closely resembles that of leprosy These circumstances will cause repeated infestation over a long time which seems to be necessary for development of the disease perhaps by eventually creating a hypersensitivity to the bacterium probably also the infecting organism may become more virulent by frequent transference (as in the case of the meningococcus)

Burack believes that the geologic condition of the soil especially humidity, is of importance too Knowledge of any possible secondary factors which enable the bacterium to invade and to thrive in the human tissue is still lacking

Infection appears to occur directly from man to man It probably takes place by inhalation of droplets from a coughing or sneezing patient or possibly by direct contact

In the described conditions nasal infection in general is very frequent in a focus of scleroma This was shown by Wolff (1934) who examined the nasal flora of a large number of otherwise healthy Bataks (the population group in northern Sumatra) with endemic scleroma and compared the results with examinations of other Indonesians most of them living in the same country

The very frequent occurrence of fecal bacteria in the nose also observed by others (it is the general experience that cultivation of *K rhinoscleromatis* from the nasal mucosa is often made impossible by growth of quickly spreading Protei on the culture media) points to extremely defective hygienic conditions Frequent introduction into the nose of the scleroma bacterium in an infected vehicle seems plausible

Perhaps the observation of many authors (Streit 1932 Elbert et al 1927) that cases of *ozena* are also frequently seen in countries where scleroma is endemic has some importance to the possibility of invasion of the *K rhinoscleromatis* in the nose The significance of atrophy of the nasal mucosa has been discussed in the section on clinical symptoms

The appearance of multiple cases of scleroma in one family is quite common and is further proof of the contagiosity of the disease

Apparently the disease has had many new victims in the last 50 years in Russia Ukraine, Poland etc although better medical supervision of the exposed population better knowledge of the disease and its diagnostic possibilities (bacteriology complement fixation test pathology) and also the development of modern surgical methods may explain a considerable part of the numerical increase in registered cases In addition World War I (1914 1918) resulted in the introduction of scleroma in places where the disease had formerly been unknown But in many countries scleroma is disappearing In Switzerland, it is diminishing in frequency rather quickly apparently through the hygienic education and improvement in sanitary conditions reaching the formerly primitive human settlements in the remote valley (Barraud 1923) In Austria scleroma has almost completely disappeared

It can thus be understood that scleroma has never been able to take root in the more civilized countries of western Europe and North America This likewise explains



Fig 199—Rhinoscleroma. Extensive infiltration of nose and upper lip.



Fig 200—Rhinoscleroma. Hebra's nose.

The epithelium is often hyperplastic with desquamation sometimes atrophic In the mucous membranes metaplasia may be observed Scanty numbers of bacteria may be present

Malignant degeneration (carcinoma or sarcoma) is very rarely seen (Szmurlo 1932)

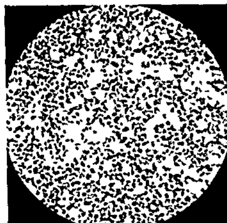




Fig 192 Fig 193

Fig 192 —Plasmocytic infiltration with many Mikulicz cells (×250) (Courtesy of E P Snijders)
Fig 193 —Mikulicz cells (×1500) (Courtesy of E P Snijders)

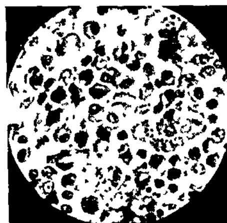




Fig 194 Fig 195

Fig 194 —Russell cells Mikulicz cells with Klebsiellae (Courtesy of E P Snijders)
Fig 195 —Capsulated bacteria in Mikulicz cells (×1500) (Courtesy of E P Snijders)

When special methods of staining (Heidenhain's hematoxylin Levaditi's silver impregnation) are applied many capsulated bacteria may be found in the Mikulicz cells and also in the interstitial spaces the *K rhinoscleromatis* In the interstice they may form large masses resembling colonies

nose often growing through the lip with formation of granulomata at the inner side The infiltration usually stops at the red margin of the lip

3 When perforation in the alveolar process of the *maxilla* occurs the teeth are loosened and expressed Growth through the hard *palate* is often seen seldom with an open perforation Small papules may develop on the gingiva The mucosa of the cheek is rarely attacked

4 The *pharynx* is often involved with formation of infiltration in the soft palate the tonsils and also other parts of the pharynx The pharyngeal are may be infiltrated and later retracted forming a sharp upper angle Deglutition is usually only very slightly impaired Synechiae between uvula and pharynx often occur The infiltration can attack the choanae the aperture becoming narrowed and sometimes completely closed Also the fornix of the pharynx can take part in the process When the opening of the Eustachian tube is surrounded by the inflammation narrowing and occlusion of the tube may follow many patients complain of buzzing in the ears and moderate deafness Very seldom the growth invades the inner ear even perforation through the ear and protrusion from the external auditory meatus has been reported In very severe cases the whole nasopharynx is closed and separated from the oral pharynx

5 Growth occurs also along the *lacrimal duct* with formation of a granuloma in the inner corner of the eye and in the lacrimal sac Sometimes a fistula of the duct exists The infiltration may proceed through the orbital fissure into the orbit with formation of exophthalmus

6 Very seldom infiltrations are found in the *tongue* sometimes as native granulomata sometimes infiltrating from the pharynx into the basis of the tongue

7 Scleroma of the *larynx* is very frequent in many countries Characteristic is the formation of subglottic infiltrations appearing as a third pair of vocal cords sometimes as a separate wedge at times attached to the cord As a result the voice becomes hoarse and later aphonic Separate infiltrations develop in the vocal cords themselves or in the wall of the larynx The granulomata may be covered with slime and crusts Stenosis may develop concentric or as a slit and suffocation is a real danger Sometimes infiltrations develop in the region of the aryepiglottic cartilage with malformation and retraction of the epiglottis Edema of the glottis and laryngeal perichondritis may develop In the larynx the atrophic form of scleroma has likewise been described often conjointly with hypertrophic processes

8 The *trachea* can be attacked according to Burack (1932) in a much larger percentage than appears from the literature The disease develops by spreading from the larynx or as primary granulomata Again circular stenosis may develop or synechiae may be found with formation of strings or membranes crossing the lumen of the trachea A place of predilection for the growth of granulomata is the bifurcation of the trachea with ingrowth in one or both *bronchi* The smaller bronchi are very seldom involved in the process

As a rule the lesions are distributed rather symmetrically although some times growth on one side and destruction and cicatrization (as described below) on the other side may be present very seldom one side only is af fected

A peculiar form of the scleromatous affection of the nose is the *atrophic* or *pseudo ozenic form* clinically resembling *o ena* Scleroma bacteria may be isolated from the nose and the complement fixation test may be positive Of course this does not mark the patient as suffering from scleroma it is pos sible that people with this condition of the nasal mucosa can become carriers more readily than other contacts with a normal mucosa Putschowski thinks that an atrophic stage nearly always precedes the development of the typical granulomatous lesions but the common occurrence of this picture is very much open to question and is denied by many authors According to Burack a care ful examination of these cases of atrophic scleroma usually reveals the pres ence of very small granulations especially at the entrance of the nasal cavity



Fig 301 —Rhinoscleroma Granuloma of upper lip and lacrimal sac

Sometimes the atrophic process is found in a patient who already shows mani fest scleromatous granulomata in the nasopharynx or larynx Others how ever believe that this atrophic mucosa is the only suitable basis for the in vasion and development of the scleroma bacterium in the human nose (Sivak 1941)

From this first localization the scleromatous process may spread along dif ferent paths

1 The *paranasal sinuses* (Highmore s antrum and frontal sinus) may be filled with granulomatous masses severe headache may be the consequence

2 Infiltration of the *upper lip* develops early very characteristic is the formation of a hard sharply circumscribed semicircular swelling under the

tissue, sometimes by ulceration and massive destruction of the tumor, followed by cicatrization In this way, a quiescent stage is reached with large external and internal defects and temporary cessation of the spread of the infection In a single patient all different stages of growth and destruction may be present at the same time

These processes cause the tumefaction to disappear locally, and by the retraction of the newly formed connective tissue new complications may arise In the nose in the later stages of the disease, a very narrow circular stenosis can be found, as a diaphragm or a funnel, consisting of very tough connective tissue, with an opening of only 1 or 2 mm Malformation of the nose and upper lip appear, as may be seen from the accompanying figures, the external nose may disappear, cicatrization of the inflammation in the pharynx, larynx, and trachea likewise can produce stenosis

The clinical picture in this stage can be indistinguishable from that of gangosa (rhinopharyngitis mutilans), but the scleromatous nature of the process can be proved by cultivation of the bacterium, by a positive complement fixation test with rhinoscleroma antigen, by a negative Wassermann reaction, and, finally, by the characteristic pathologic changes in tissue recovered by biopsy from a still active portion of the lesion

From this description it will be plain that the clinical picture can present a great many different aspects Burack, especially, who compiled the descriptions from literature before 1932, gives a very complete list of all possibilities

The clinical picture seems to differ in different countries in Sumatra, Snijders (1931), Kouwenaar et al (1934), and Oomen and Kirschner (1938) found destructive processes not uncommon, whereas Burack rarely observed them on an extensive scale in eastern Europe The chief localizations of the disease may likewise vary, as may be gathered from Table XX, showing the frequency of the different localizations of the disease

TABLE XX

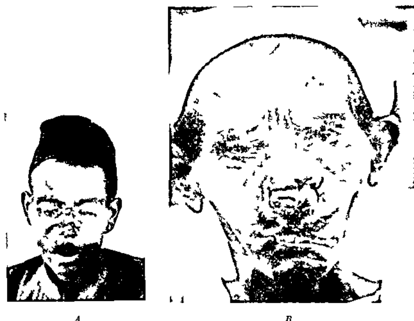
A C T N... ...TIONS					...a Lehm Poland Lwow 457
LOCALIZATION (%)					
Nose	74 1	56 8	72 9	84 6	75 0
Pharynx	51 3	24 5	25 7	27 2	30 0
Nasopharynx	57 2	63 0	60 0	62 9	?
Larynx	72 4	81 7	58 5	62 9	70 0
Trachea	35 0	27 4	?	13 2	6 7
Bronchi	16 3	4 4	?	7 6	1 1

These statistics contain particulars of large numbers of patients all originating from eastern Europe (Poland and the U S S R) The frequencies of observed cases of scleroma of the larynx and especially of the trachea and bronchi differ considerably This difference may be explained, at least par

9 According to the majority of the authors the *cervical lymphatic glands* are enlarged in most cases This may be partly due to the secondary infection following ulceration but several authors (Rona 1899, Sercer 1932) could cultivate the Klebsiella from the glands Pathologic examination showed only subacute unspecific inflammation

The granulomata may grow for many years the spread of the process through the tissues as a rule is very slow but sometimes very rapid growth can be observed Ultimately a serious malformation develops in many cases resulting in the typical Hebra s nose laryngeal stenosis etc

The patients do not suffer unduly from the disease and for a long time disturbances in general health are only slightly marked Complaints of nervousness cold hands and feet and menstrual disorders are often reported



A *B*

Fig 0? —*A* and *B* Rhinoscleroma. Destruction and cicatrization

Comparatively little is known regarding microscopic and biochemical changes in the blood Burack (1932) saw leucocytosis in 10 per cent of his cases only and shift to the left in 60 per cent Severe anemia seldom occurs The sedimentation rate is sometimes high A rise in the calcium and potassium (Kahn 1927) and cholesterin level and an increase of the pH of the blood have been observed especially in severe cases

Emphysema emaciation anemia and finally cachexia are not infrequently found in the final stages in cases with stenosis

In the course of the years many cases show a decrease in size of the granulomata usually by retraction due to the formation of more connective

DIAGNOSIS

The diagnosis is based on the following criteria

1 Clinical Picture

In the majority of cases, the malformation is very typical Physicians with knowledge of the disease can easily differentiate this from tumor, lupus lues, frambesia or leprosy, diagnosis of the last two diseases is frequently made in the tropics by those not familiar with scleroma The residual forms with cicatrization or massive ulcerations may closely resemble lupus or rhino pharyngitis mutilans (gangosa, frambesia) In true gangosa, however, the Wassermann reaction is nearly always positive Polyps of the nose are much softer, they are pedunculated and have a different appearance The initial and *atypical forms, like the atrophic form, are difficult to evaluate, and here* other diagnostic means are of greater importance For a definite diagnosis positive results of the following examinations are necessary

2 Bacteriologic Examination

The Klebsiella must be cultivated from the deeper layers of the tissue, but with this precaution they are found in a large majority of the cases A positive culture greatly supports the diagnosis, however, carriers exist among the immediate contacts of the patients

3 Complement Fixation Tests

The complement fixation reaction was first described by Goldzieher and Neuber (1909), and later confirmed, the technic has been modified by many investigators An extract of *K rhinoscleromatis* is used as antigen According to the general experience, this reaction if performed with sufficient care, is specific Neuber and Adam (1934) saw a positive reaction in 80 to 90 per cent of the manifest cases, Wolff (1934) in 92 5 per cent, Guerkesse and Aloukère (1935) in 95 per cent Unspecific reactions occur rather seldom, Wolff, e g, found them in only 1 per cent of 501 controls According to Alooker (1941) a negative reaction in a suspect patient can be converted into a positive reaction by intravenous injections of tartar emetic

Besides the manifest cases, positive reactions are also found in a number of people *living* in close contact with these patients, just as is the case in finding Klebsiellae It is still un*certain* whether a person with a positive complement fixation reaction is indeed suffering from the disease, that is, developing anatomical lesions, or whether these have developed before It also seems possible that a carrier may develop a positive complement fixation test

The only other disease in which a positive test with scleroma antigen sometimes occurs is *ozena*, Wiraboff (1929) saw 7 per cent positive reactions among 57 patients However, these observations were made in a geographic focus of scleroma, and secondary infection with *K rhinoscleromatis* was found in 6 per cent of his *ozena* patients, 2 of these carriers also had a positive complement fixation test Indeed, *K ozaenae* may have some capsular antigen and even body antigen in common with *K. rhinoscleromatis*

The complement fixation reaction, then, is usually positive in the patients Sometimes contacts are found with a positive reaction but without distinct scleromatous lesions In those cases doubt exists whether these are patients with scleroma or are healthy carriers, contact with the bacterium having re

tially, by a varying thoroughness of the examination But this cannot explain all, for the figures regarding localizations in other organs likewise show marked differences The reason for these differences are unknown, Burack mentions climate and social circumstances

Generally speaking, the cases reported from tropical countries are few and scattered Statistics of Kouwenaar et al (1934) are somewhat different Among 55 cases in Bataks in Sumatra, they saw, in 100 per cent, affections of the nose, in 17 6 per cent, of the pharynx and nasopharynx, and only once a dubious lesion in the larynx One must remember however that all these observations were made in the field under primitive conditions, and that only a part of the patients were examined by an expert laryngologist It is therefore probable that cases of scleroma of the larynx have been overlooked However, it is very striking that the observers did not find a single case of scleroma in which the process had given rise to more or less serious complaints of laryngeal disturbances, dyspnea, stenosis, or even aphonia, and also that on questioning neither the physicians practicing in the endemic area nor the population had any knowledge of patients with these complaints or of any who had died of suffocation Neither do other authors describing scleroma in Indonesians, mention laryngeal involvement, among the extensively published cases (about 100), slight and dubious lesions from the larynx were present in only 3 It seems indeed probable that a difference exists and that scleroma respiratorium in Indonesians has less tendency to attack the larynx and trachea than is the case in Europe

Scleroma respiratorium is a very chronic process, the disease can last for many years It is a disease of young adults, 70 to 80 per cent of the cases observed for the first time occur between the ages of 20 and 35 years, but possibly these infections have existed for many years Children may also be affected The youngest patient observed was 2 years and 7 months old (Burack) According to all statistics, incidence in women is higher than in men (58 5 per cent and 41 5 per cent, respectively, in Belinoff's inclusive statistics, in Indonesia the literature contains descriptions of the disease in 74 women and 31 men patients)

Nothing is known about the period of incubation, nor is it known how the disease is acquired The first symptoms in many cases are likely to cause such slight complaints that the patient is first seen and the diagnosis made many months or even years after the beginning of the disease

Once the infection has begun, the disease may progress slowly for many years, causing granulomata of ever increasing size and number and attacking other regions of the respiratory tract Patients who have had the disease for more than 50 years have been observed (Burack) The prognosis *quoad vitam* is usually favorable, the general health is only slightly impaired There is danger of stenosing processes developing in the larynx, trachea, or bronchi, but if treatment is adequate to maintain the possibility of respiration (by tracheotomy, for instance), life can again be prolonged for years

ported As stated above, focal reaction may be observed even after the nostic intracutaneous injection of Klebsiella, and long continued admir tion of these bacterial suspensions may bring about complete disappea of the granulomata If no success is obtained, preliminary injectio Solganol may be necessary (see skin reaction) Recently Neuber (1941 Belinoff (1941) advised alternating treatment with vaccine and gold pre tions combined with transfusions of blood or serum of convalescent pat

Treatment by drugs has been tried with a large number of preparations cess has been reported from the use of tartar emetic or gold injections p ably in combination with injections of vaccines Reyes (1946) recomn azosulfamide Devine et al (1947) noted disappearance of all clinical toms after 2 months of treatment with streptomycin, the patient recei *total dose of 97 25 Gm of that antibiotic No relapse was seen with* months More experience with these newer remedies is needed

In those cases where the growth of the granulomata, secondary cica tion, or even acute glottis edema endanger life by suffocation, surgical vention will be indicated Stenosis of the larynx or of the upper tr sometimes can be relieved by intubation, but usually the effect is unsati tory and tracheotomy or laryngofissure with removal of the growth electrocoagulation is necessary Plastic operations may be helpful Als stenosing process in the nose, the malformation of the pharynx, and ste of the choanae can be managed surgically Large external tumors ca *ablated Local application of dry ice is advised The prognosis of sur* treatment is uncertain in some patients growth of new granulomata ne tates repeated operations, in others destruction and cicatrization hel diminish the symptoms, and life can be prolonged considerably

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sulted in production of antibodies but not in the development of clinical and anatomical symptoms An unspecific reaction is of rare occurrence

The reaction is a very valuable aid in the diagnosis of scleroma Especially in epidemiologic investigations (field work) has extensive use been made of this test

4 Agglutination Test

Agglutination tests with *K rhinoscleromatis* have given inconstant results and have not yet found extensive use According to Neuber and Adam (1934) and Guerkesse and Aloukere (1935) the agglutination test is very specific the latter authors found that the results parallel the complement fixation reaction in 45 out of 52 cases It is necessary to use the bacterial variant without a capsule

When more satisfactory technics are developed the agglutination reaction will probably prove of more importance than at the present time

5 Intracutaneous Allergic Test

*Neuber (1933) saw that a positive cutaneous reaction appears after intra*cutaneous injection of a suspension of the Klebsiellae (prepared by treating dried bacteria with ether) together with a focal reaction The observation however must be prolonged for at least 8 days the reaction occurring during the first 3 days being nonspecific No positive reactions were seen in cachectic patients According to Neuber these patients can be temporarily anergic to the bacteria after injection of a gold preparation (Solganol B Oleosum—Schering) they became allergic and the reaction positive Kuilman et al (1937) also saw satisfactory reactions but other authors could not report consistent results

The intracutaneous reaction needs more confirmation but will probably become a useful adjuvant to the diagnosis

6 Histologic Section

The characteristic pathologic picture in tissue removed by biopsy is usually clear enough to preclude any doubt

TREATMENT

No unanimity of opinion exists as to the best methods of treatment of scleroma Good results have been reported following treatment with x rays or radium often the granulomata decrease in size and are absorbed for the greater part One danger is the formation of cicatricial tissue in the larynx with stenosis and danger of suffocation Radiation must be applied repeatedly for a long time to prevent relapses Reyes (1946) gives 7 applications of roentgen rays (200 KV filter 0 5 mm copper and 1 mm aluminum focal distance 50 cm dose 200 r per day) for 7 consecutive days and repeats these courses of radiation several times over a 2 year period

Administration of polyvalent vaccines made from *K rhinoscleromatis* has been developed by Neuber and very satisfactory results have been re

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Key to Family Rickettsiaceae Pinkerton, 1936*

Small bacteriform microorganisms, *often pleomorphic, gram negative,* with staining properties *sui generis,* obligate cellular parasites with distinct grades of specific adaptation for arthropod hosts and susceptible animals

I Obligate cellular parasitism in the sense of not multiplying in the absence of living tissue, not necessarily intracellular

A. Host and vector *Ixodidae,* facultatively intracellular
  Genus I — *R burneti* Derrick, 1939
  R diaporica Cox, 1939
B Vector *Pediculidae,* extracellular
  Genus II — *R wolhynica* Töpfer, 1916
  R weigli Mosing, 1936

II Obligate intracellular parasitism

A. Pathogenic in variable degree for the arthropod vector and for mammals
  Genus III — *Rickettsia*
  R prowazeki da Rocha Lima, 1916
  R mooseri Monteiro, 1931
B Not pathogenic for the arthropod vector (or host)
  1 Pathogenic for mammals
   (a) Host and vector *Trombidiidae*
   Genus IV — *R orientalis* Nagayo et al, 1930
   (b) Host and vector *Ixodidae*
    aa Intracytoplasmic
   Genus V — *R ruminantium* Cowdry, 1925
   R canis Donatien and Lestoquard, 1936
   R ovina Donatien and Lestoquard, 1936
   R bovis Donatien and Lestoquard, 1936
    bb Intracytoplasmic and intranuclear
   Genus VI — *Dermacentroxenus* Wolbach, 1919
   D rickettsi Wolbach, 1919
   R conori Brumpt, 1932
   R pijperi Amaral and Monteiro, 1932
  2 Nonpathogenic for mammals
   (a) Localization in various tissues and organs of the arthropod host, at times causes formation of mycetomas
   Genus VII — *R ctenocephali* Sikora, 1918
   R lectularia Arkwright et al, 1921
   (b) Localization in a single organ, tissue, or cell type
   Genus VIII— *Wolbachia* Hertig, 1936
   W pipientis Hertig, 1936

The entire systematization of the rickettsial group was revised by Macchiavello (1945)

Subsequent to the preparation of this chapter, a new rickettsial disease was described under the name "rickettsialpox" (Refer to Chapter 36)

The etiologic agent of rickettsialpox is *R akari* Huebner, Jellison, and Pomerantz, 1946 *R akari* is morphologically similar to *R prowazeki* and *R mooseri,* diplococcal and diplo bacillary forms have been found It stains well with the Giemsa and the Macchiavello methods but poorly with methylene blue or the Gram stain

Rickettsia burneti and Rickettsia diaporica (the American variety of the *former)* — Cox (1938) described them as lanceolate or bipolar bacilli sometimes diplobacillary some time filamentous Within the cells, in the cytoplasm, are found isolated bipolar or diplo

*Editor's note (O F) Bergey's *Manual of Determinative Bacteriology* (1948) classifies the completely studied Rickettsiaceae which are pathogenic for man as *Rickettsia prowazekii R typhi R rickettsii, R conorii R tsutsugamushi R akari,* and *Coxiella burnetii.*

CHAPTER 35

RICKETTSIOSES OR RICKETTSIAL DISEASES

ATILIO MACCHIAVELLO

(TRANSLATED FROM SPANISH INTO ENGLISH BY ANTHONY DONOVAN)

GENERAL CONSIDERATIONS

Diseases generally classed under the heading "typhus fevers" (or *typhus group of fevers* of English authors) are caused by *rickettsias* and therefore are included under the general heading "rickettsial diseases" or simply "rickettsioses"

RICKETTSIAS

Rickettsioses are diseases caused by rickettsias Pathogenic rickettsias however form only a small group of the large family of Rickettsiaceae Pinkerton 1936 which includes microorganisms interposed between bacteria and filtrable viruses similar to *R prowazeki* described and named by da Rocha Lima 1916 the type species Like bacteria the rickettsias have a definite morphology with perfect individualization of each element Under the electron microscope is seen a limiting cellular membrane quite distinct from the internal protoplasm (Plotz Smadel Anderson and Chambers 1943 Weiss 1943 Mudd and Anderson 1945) They differ from bacteria in that they are not able to live independently—for example in bacteriologic cultures—since preformed substances produced by living cells are necessary for their development (This shows that the enzyme system of the rickettsias is incomplete) They must like filtrable viruses live intracellularly This dependence is not as rigid as it is with viruses for some of the rickettsias live extracellularly like *I burneti* and *R quintana* or *wolhynica* although with definite dependence upon the metabolism of certain types of cells Their intracellular life demands that they be related to hosts and reservoirs and when pathogenic to vectors There is a tendency to accept as true rickettsias only those related to an arthropod host temporary or permanent the permanent host being the natural reservoir Other reservoirs are found among the higher vertebrates especially rodents

The same rickettsia may show different grades of adaptation for different arthropods or mammals When the adaptation to an arthropod is perfect the rickettsia is hereditary when it is imperfect the insect becomes ill and may die as in the case of *Pediculus humanus* infected with *R prowazeki*

Our knowledge of rickettsias is incomplete definition and classification is therefore difficult It is understandable that the pathogenic types are the best known

THE RICKETTSIAS AND THEIR CLASSIFICATION

TABLE XXI CLINICAL ETIOLOGIC CLASSIFICATION OF THE RICKETTSIOSES

ETIOLOGIC AGENT	GROUPS OF RICKETTSIOSES (CLINICAL CLASSIFICATION)	DISEASES COMPRISING EACH GROUP
	I *Nonexanthematic rickettsioses or with evanescent exanthemata*	
1 *R burneti*	1 Not recurrent	Australian "Q" fever
R diaporica		American "Q" fever
2 *R wolhynica*	2 *Recurrent*	*Trench fever or quintana fever*
	II *Exanthematic rickettsioses*	
	A *Human*	
3 *R prowazeki*	1 Petechial exanthematic rickettsiosis	Classical exanthematic typhus fever—Brill's disease
R mooseri		Exanthematic murine typhus
4 *D rickettsi*	2 Macular exanthematic rickettsiosis	Spotted fever
R conori	3 Boutonneuse exanthematic rickettsiosis	Boutonneuse fever
R pijperi		South African tick fever
5 *R orientalis*	4 Maculopapular exanthematic rickettsiosis	Scrub typhus
	B *Animal*	
6 *R ruminantium*	1 Reticuloendothelial rickettsiosis	Heartwater disease of cattle
7 *R canis*	2 Monocytic rickettsiosis	Canine typhus

The foregoing clinical classification does not consider epidemiologic variants nor virulence nor geographic localization which are apart from clinical criteria.

TABLE XXII RELATIONSHIP BETWEEN THE RICKETTSIOSES

RICKETTSIOSES	INITIAL ULCER	EXANTHEMA	VECTOR	WEIL FELIX REACTION	SPECIFIC COMPLEMENT FIXATION TEST
1 Nonexanthematic and nonrecurrent rickettsioses					
"Q" fever	0	0	Not necessary	0	Yes
2 Recurrent rickettsioses					
Trench fever	0	0	Louse	0	?
3 Exanthematic rickettsioses		0			
a Petechial					
Classic exanthematic typhus	0	Petechial	Louse	OX19+++ OX2+	Yes
Murine typhus	0	Petechial	Flea and rat louse	OX19++ OX2+	Yes
b Macular					
Rocky Mountain spotted fever	0	Macular	Tick	OX19+ OX2+ OXK+	Yes
c Papular					
Boutonneuse fever	+	Papular	Tick	OX19+ OX2+	Yes
d Maculopapular					
Scrub typhus	+	Maculopapular	Mite	OXK+++	Yes

bacillary forms or groups of rickettsias in rounded masses although some of these masses may show less different stated organisms of a coccoidal or granular type In animals as well as in tissues or egg cultures the organism grows and develops well extracellularly. Morphologically it is similar to *R prowazeki* although somewhat larger which may be due to the fact that it stains more intensely with Giemsa and with the Macchiavello stain

Rickettsia wolhynica—The morphology in mammals is diplococcal or diplobacillary and in lice in addition oval or round with polar staining (Töpfer) larger more nearly oval shorter thicker and at the same time less pleomorphic than *R prowazeki* The organisms are grouped in layers or palisades on the intestinal epithelium of the louse for which they are not pathogenic It stains more easily and more intensely than the rickettsia already mentioned It is not known for certain whether or not it is hereditary in the louse

Rickettsia prowazeki and Rickettsia mooseri—In mammals it is paired coccoid or lanceolate (Wolbach Todd and Palfrey 192) In lice it is extraordinarily pleomorphic according to da Rocha Lima In tissues (cultures) it is paired lanceolate and less frequently filamentous (Nigg 1930 Zinsser and Macchiavello 1936) With Giemsa stain it usually shows a halo and in the so called multiplying forms demonstrates red and blue staining material In peritoneal exudates of rats and in tissue cultures the author has observed filamentous forms of 1 and 1 microns and longer There is no morphologic difference between *R prowazeki* and *R mooseri* although the latter is more diffused in the tissues of susceptible animals and grows more easily in tissue cultures As with all the rickettsias except *R burneti* and its variant *diaporica* it is not filtrable It is not hereditary in the louse which it dies when the parasitization of the epithelial cells of the digestive tract produce distention rupture and desquamation of the tract In mammals it lives in the cytoplasm of the endothelial cell The murine variety prefers the serosal cells of the tunica vaginalis of rats The typical cellular form was described by Pinkerton in 1936 and before as a growth en masse of organisms It has been cultivated in the louse by Weigl (1920) in tissues the plasma by Wolbach and Schlesinger (1923) Zinsser and Batchelder (1930) and Pinkerton and Hass 1931) in cultures by Maitland and modified Maitland method by Nigg and Landsteiner (1930 1931) Hilgler and Aschner (1934 Zinsser and Macchiavello (1936 in the agar Zinsser Weiss and Fitzpatrick (1938 1939) in eggs by Cox (1939) in the vitelline sac and on the chorioallantoic membrane by Zia (1934

Dermacentroxenous rickettsia—In mammals it is paired frequently surrounded with a halo in lanceolate form with or without polar granules and rounded In the tick it is more pleomorphic and with the bacillary form type without chromatoid granules are found lanceolate diplobacilli and small intranuclear rods with chromatoid granules (Wolbach et al 1922) The lanceolate type is similar to and has large as a pneumococcus and is not like the form of *R prowazeki* In ticks it is found all through the tissues In tissue culture Pinkerton (1936 found multiplication scant in the cytoplasm but abundant in the nucleus the morphology being distinct for each localization To the three types described by Wolbach a fourth (Spencer and Parker 1940) has been added This is not infectious but produces immunity

R brasiliensis is synonymous with *D rickettsi* *R conori* of boutonneuse fever and *R pijperi* of South African tick fever are morphologically similar to *D rickettsi*

Rickettsia orientalis—This is a short diplobacillus with bipolar staining (0 3 to 0 by 0 8 to 2 0 microns) It grows diffusely in cell cytoplasm but does not distend the cells It can be seen easily if the anterior chamber of the eye of experimental animals is inoculated and Descemet s membrane examined It does not grow intranuclearly

Attempts to classify the rickettsial diseases have been numerous some being clinical (P Jorge 193
some utilizing
the primary tr
multiple criteria such as epidemiology pathology serology immunology clinical characteristics etc among them being those of Amaral and Monteiro (1931) Brumpt and Deutschman (1936) Burnet (193) Zinsser (193) Castañeda (1942) and Plotz and Wertman (1945)

As was to be expected, America could not be kept free from typhus, and first the *Conquistadores* and later the colonists and immigrants were the cause of serious epidemics. In Mexico the disease has been recognized since 1530, in Chile since 1554 (Rosales), in Colombia since 1630 ("the plague of Santos Gil"), in Peru since the beginning of the Conquest. In Canada and the United States, it is mentioned in Quebec and Montreal, 1820, Halifax, 1827, Boston, 1838 and 1847, New York, 1818, 1825, 1837, 1852, 1861-65, 1881, and 1892, Philadelphia, 1827, 1836, 1847, 1864, and 1880, New Orleans, 1847, with some recent epidemic outbreaks in Iowa (Boyd, 1917), California (Cumming and Senftner, 1917), and New Mexico (Armstrong, 1922), the latter possibly originating in Mexico. Among the Indians of South and Central America, as in Mexico, typhus is endemic; not so in the United States, where there is mentioned only one serious outbreak, among the Navajo Indians, on the San Juan Reservation, New Mexico, 1920-1921.

In Africa, typhus has occurred since time immemorial in the northern Mediterranean zone. Recently, in Uganda (1932), Transvaal, Union of South Africa, and in Basutoland, important outbreaks have occurred. In Asia, typhus has been definitely recognized only recently.

The enormous number of references available in relation to classical exanthematic typhus contrasts with the scanty information to be found on the other rickettsial diseases, with reference to history as well as incidence. This is understandable, as most of the rickettsias are local diseases of an endemic or sporadic character, without much influence on the political, social, or economic lives of the people, and without dramatic aspects which spontaneously attract attention.

In 1837 (Gerhardt), typhus was definitely distinguished from typhoid fever (Stille, also, 1838), this being the first decisive advance in the study of rickettsial diseases.

Palm (1878) and Baelz and Kawakami (1879) described for the first time Japanese river fever, although it is supposed that the disease (tsutsugamushi) had been known for 1,000 years. Ten years later Maxey (1899) identified Rocky Mountain spotted fever, although about 1873 it had been described in the vicinity of the Snake River, Idaho.

There were established, then, the three predominating groups of exanthematic rickettsioses, although their etiologic relationship was not realized at the beginning, nor were they always clinically differentiated in the places where they existed together. Spotted fever, in the United States, was the first rickettsiosis in which important results were obtained in experimental studies. In 1902, it was observed in the Bitterroot Valley of Montana, with a high mortality, of 70 to 80 per cent. Wilson and Chowning immediately proved *Dermacentor andersoni* as its transmittor, a supposition confirmed by McCalla (1905) who transmitted the disease from man to man by ticks removed from patients, and by Ricketts (1906) who in turn transmitted it to laboratory animals—monkeys and guinea pigs—being unaware of the experiment already mentioned, which was not published until 1908. Previously (1906), Ricketts had proved the susceptibility of these animals to spotted fever, in 1907, he demonstrated the hereditary character of the infection in ticks, and, in 1909, he believed that he saw the specific infecting microorganisms in the blood of human beings, guinea pigs, and monkeys with the disease and in the tissues of the vector.

Nicolle, Comte, and Conseil (1909) demonstrated that typhus is transmitted by lice, and also showed the susceptibility of guinea pigs and monkeys to experimental infection, facts confirmed by Ricketts and Wilder (1910) while working with Mexican typhus *(tabardillo)*. Again they thought they could see the etiologic agent of typhus in preparations from the blood of patients and from the intestinal contents of lice. By means of cross immunity experiments they showed that typhus and spotted fever are different diseases. From 1898 until 1910-1911, Brill, in a series of notable studies, emphasized the epidemiologic and clinical differences between typical exanthematic typhus and cases of the disease which today bears his name, sporadic cases seen in New York and Boston, which Anderson and Goldberger (1912) proved to be attenuated forms of typhus.

During the following years, experiments were concentrated on the etiologic agent of typhus, 30 or more microorganisms being suspected. It is possible that Hegler and Prowazek

HISTORICAL NOTES ON RICKETTSIAL DISEASES

GEOGRAPHIC DISTRIBUTION

The rickettsial disease group has been increasing continuously while at the same time investigative methods have been improved, particularly those related to the etiology

No clinical or epidemiologic description extant assures us that the rickettsioses were known by Hippocrates or other physicians of ancient times In the Cronica Cavense of the year 1083 (a monastery near Salerno), there is mentioned "a fever accompanied by petechias," the first reference which makes one suspect exanthematic typhus Up to 1490, in Spain, typhus played a prominent role in the war between the Saracens and the Spaniards, and during the siege of Granada, typhus broke out in epidemic form, taking a toll of 17,600 victims among the soldiers The medical historians of the period (Luis de Toro, 1574, López de Corella, 1574 Mercado, 1574, Carmona, 1582 Pérez 1590, Martínez de Leiva, 1597, Bocungelino, 1600, and Soria, 1635), whose works have been reviewed by Villalba (1802), believed that typhus was introduced into the Iberian peninsula by Spanish soldiers infected on the Isle of Cyprus, from then on giving rise to a great number of epidemic outbreaks and extending to America in Mexican territory simultaneously with the conquests of Hernán Cortéz

In 1546, Geronimo Fracastorio described typhus in a masterly manner in Chapter VI of Volume II of "*De Contagione*," referring to the epidemics in Italy during the years 1505 and 1528 Zinsser (1935) stressed the importance of this episode, saying "In 1530, Charles V was crowned ruler of the Roman Empire at Bologna, by the power of typhus fever"

The relationship of typhus to war, famine, migrations, political, social, and economic upheavals, and other public calamities was early recognized in history Charles V, himself, in 1552 was forced to give up the siege of Metz because his army was greatly reduced in numbers by typhus From 1618, the beginning of the Thirty Years' War, until 1630, typhus dominated the entire continent of Europe In Hungary, its incidence was such that it was called *morbus hungaricus* Its frequency in political prisons gave it the name *morbus carcerorum* Lazarus Riverius (1623) described the first epidemic in France, in Montpellier, as *febris maligna pestilens*, which was repeated in Lyons and Limogès, in 1628 (with 60 000 and 25 000 deaths, respectively), in Poitiers in 1651, and in Burgundy in 1666

In England from the first, typhus was associated with prisons (jail fever), and the judgments against prisoners parasitized with lice (*Black Assizes*) caused repeated epidemics, such as the well known epidemic at Oxford University in 1577, which cost the lives of 510 persons, among them 100 members of the University In 1643, according to Willis, it destroyed great numbers of individuals in Parliament and the Royal Army during the siege of Reading In Ireland the so called *Irish ague* occasioned the outbreak of Cork, 1708, and later the epidemics of 1718, 1729, 1735, 1740, and 1797 During the entire eighteenth century, typhus scourged Europe Moscow in 1730, Germany in 1740, Flanders in 1743, Spain in 1762, Naples in 1764 During the Seven Years' War, the French Revolution, the Crimean War, the Napoleonic campaigns, especially that in Russia, and later, during economic depressions in Silesia, 1846, and London 1862, typhus greatly reduced in numbers the armies and civilian populations until the middle of the nineteenth century, when it began to decline In the Franco Prussian War it had a secondary role Finally it was restricted to the Balkans and Russia until World War I in 1914

Typhus began in Serbia with extraordinary virulence At one time 2 500 cases were isolated daily in military hospitals alone In the postwar period, it is calculated that there were between 6,000 000 and 10,000,000 cases in Russia within 4 years

Advances in the prophylaxis of the disease were seen during the Italian conquest of Abyssinia, where African troops, according to Castellani, had more than 20,000 cases, with not a single one among the European troops World War II is another example of the fact that typhus is no longer necessarily a disease of armies Statistical data, on the other hand, show the damage it still does among civilian populations of belligerent or occupied countries

Japanese river fever and investigations on the larvae of *Trombicula akamushi* the red mite (Ashburn and Craig, 1908, in the Philippines, Breinl, Priestly, and Fielding, 1914, in North Queensland, Dowden, 1915, in the Malay States, Hatari, 1921, in Formosa, Lagrange, 1923, in Annam)

By 1926 the studies of Maxcy managed to break the unity of exanthematic typhus, which had not been destroyed by the researches of Brill On epidemiologic grounds he showed that the endemic typhus of the southern part of the United States has a direct relationship with rats and their ectoparasites Mooser (1928) established a diagnostic sign in guinea pigs inoculated experimentally with virus of Mexican typhus (Mooser's sign) Dyer et al (1931) obtained murine virus from fleas of rats caught in Baltimore, and Mooser, Castañeda, and Zinsser (1931) obtained murine virus from brains of rats trapped in the prison of Belen, Mexico The former transmitted the infection from rat to rat by means of fleas, and the latter by means of rat lice Murine virus is obtained in the most diverse countries, in Syria, Greece, Tunis, Chile, Manchuria, Malay States, Russia, etc At first the endemic character of murine typhus caused it to be confused with the sporadic disease described by Brill, this was clarified by the work of Zinsser (1934), who proved the classical nature of the disease in the northeastern part of the United States and characterized it as recurrent typhus At first, the lack of comparative studies of the various viruses discovered gave rise to new terminology, generally of a geographic character, causing much confusion, on the one hand, and on the other, demonstrating the incorrectness of considering Mexican typhus as the equivalent of murine typhus The designation *endemic typhus* for the recently discovered disease and *epidemic* for classical typhus also appeared to be inadequate when it was considered that the murine virus could become epidemic if implanted in man and transmitted to other individuals by means of lice Zinsser thought that if, originally, typhus was a disease of rats, and that if the latter invaded Europe only with the return of the Crusaders (as the first unmistakable reference to rats is made in the works of Giraldus Cambrensis, 1147 1223), it is entirely possible that the epidemic typhus of the Middle Ages and of today is really a new disease of mankind, which would explain why it is not mentioned in ancient classical medical treatises

In its turn, Rocky Mountain spotted fever also lost its unity when, in 1930, the so called "Eastern type" was discovered, in contrast to the classical type of the West In 1932, Reimann, Ulrich and Fisher mentioned the Minnesota variety In 1928, Piza, Meyer, and Gomes first described the typhus of São Paulo In 1933, a similar affection was reported in Minas Geraes In 1935 Pijper and Dau studied African tickbite fever Patiño, Afanador and Paul described, in 1937, a focus of petechial fever in Tobia, Colombia Recent laboratory studies indicate that all these diseases represent at most simple variants of Rocky Mountain spotted fever, and, including boutonneuse fever of the Mediterranean, have close generic connections with it (Parker and Davis, 1933, Dyer, 1933, Badger, 1933, Haas and Pinkerton, 1936, Amaral and Monteiro, 1931, Monteiro, 1933, Dias and Martins, 1937, etc)

In connection with tsutsugamushi, scrub typhus, and other variants of the fevers transmitted by mites, the investigations of Lewthwaite and Savoor (1936), as well as the recent studies of American Army doctors stationed in the Far East, should be mentioned as being outstanding in determining the unity of the group and the local variants

During recent years we have witnessed a better understanding, as well as a greater extension, of a curious disease, "Q" fever, which should more properly be called "burnetiosis" Discovered in Australia, as a disease associated epidemiologically with ticks and rodent vectors, it has been finally determined to be a sickness transmitted principally from man to man, giving origin, at times, to explosive epidemics of atypical pneumonias, often called "Balkan grippe"

Also, while World War II afforded new and unexpected fields for the investigation of rural typhus (scrub typhus, tsutsugamushi fever) in the South Pacific theater of operation in the heart of New York City there appeared a new rickettsiosis, resembling in appearance chicken pox, which forms by itself an entity unmistakable among its analogous diseases—rickettsialpox The history of this disease is instructive and offers a field for interesting speculations, on which, unfortunately, we cannot enlarge in this place (See Chapter 36)

(1913), Sergent, Foley and Vialatte (1914) and Nicolle, Blanc and Conseil (1914) saw the organism in the feces of lice collected principally on individuals with typhus, but the merit of describing, naming and proving the etiologic role of *R. prowazeki*—so named in honor of the two martyrs to typhus, Ricketts and Prowazek—belongs entirely to da Rocha Lima. Da Rocha Lima created the genus *Rickettsia* and clearly defined its morphology, its connection with the louse vector, its staining properties, its differentiation from the bacteria, the stages in its intracellular development in the intestinal cells of the louse and the relationship of this coexistence with human infection.

The studies of da Rocha Lima represent a notable contribution to our knowledge of rickettsial disease and an example of scientific work carried out without any vacillation in the face of a great many contradictory conditions, many of which at the time appeared to be true. In reality, during the period 1914 to 1916, in the midst of World War I, the opportunities for working on typhus increased, but at the same time investigations were complicated by a series of scientific discoveries quite difficult to interpret. Plotz (1915) had described as the etiologic agent a microorganism which seemed to fulfill all the requirements for specificity. Nicolle proclaimed the possibility that typhus was an infection caused by a filtrable virus. Various authors denied or doubted the bacterial nature of rickettsias or of their pathogenicity. Experiments on lice were made difficult by the lack of knowledge of the histology and biology of the insect and also by the contamination of the colonies with nonspecific and nonpathogenic rickettsias (*R. pediculi*). The Weil-Felix reaction lent support to the suggestion of an etiologic connection between typhus and *Proteus*. Last, trench fever and its possible cause, *R. wolhynica* or *quintana*, a parasite of the louse, added more confusion to that already mentioned. During that period the knowledge of rickettsias was broadened by the successive and rapid discoveries of new species (*R. melophagi*, *R. lectularia*, *R. ctenocephali*, etc.), these findings culminating with the work of Cowdry (1923, 1925) and of Wolbach and his school. Wolbach (1919) established definitely the etiologic role of rickettsia in spotted fever, creating and defining the new genus *Dermacentroxenus*, and in 1922, with Todd and Palfrey, contributed irrefutable proofs for establishing the specificity of *R. prowazeki* as the cause of typhus. In addition, his notable studies in pathology amplified the classical work of Popoff (1875), Fraenkel (1914, 1915), Prowazek (1915), Aschoff (1915), Ceelen (1916), Jaffé (1918), Grzywo-Dabrowski (1918), Herzog (1918), Nicol (1919), Spielmeyer (1919) and many others and demonstrated the presence of rickettsias in the typical lesions (1920, 1922).

During the decade 1910-1920 five other important events merit being mentioned. The first was the discovery of a new exanthematic disease, nodular scarring fever, recognized by Conor and Bruch (1910) in Tunis and later found at numerous points on the coast of the Mediterranean and finally found to be identical with Kenya fever. The second was the opportunity offered by World War I (1914-1918) to prove epidemiologically the role played by the louse as vector of typhus and to base prophylaxis on measures for eradicating this parasite. The third was the incorporation of the Weil-Felix reaction, using *Proteus* OX, in diagnostic measures for typhus, a reaction which has been extended to the other exanthematic rickettsioses and which, thanks to the accidental finding of the Kingsbury strain, served later on in the hands of Felix and Rhodes to form the basis for a serologic classification of the diseases of this group. (Incidentally, the antigenic nature of rickettsias was surmised by means of comparative studies with *Proteus* X.) The fourth event was the discovery and description of trench fever (quintana or Wolhynian fever), possibly caused by *R. wolhynica*, a disease which reached epidemic proportions between 1915 and 1918 among the warring armies. Recognized first in Flanders and France by Graham, Hunt and Rankin, it soon was found in Poland, Austria, Italy, Greece, Egypt and elsewhere. Although experiments demonstrated

lead to no positive conclusions as to the true nature of the disease and its relationship with other rickettsias. Finally, it is important to note in this decade another event of no less value than those already mentioned, the multiplication of studies on diseases similar to

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Techniques used in the study of the rickettsioses have undergone radical changes and have been enriched with methods more exact than those of scarcely 20 years ago, when the Weil Felix reaction and animal inoculation dominated this field

The veritable chaos which existed only 10 years ago with regard to classification of the rickettsial diseases and relationships among them is disappearing, thanks to application of the methods of investigation mentioned above To Megaw must be accorded the honor of being possibly the first to suggest a logical grouping and classification of the rickettsioses Definitive classification will come with more detailed knowledge of the antigenic constitution of the rickettsias and of their mutual inter relationships

CLINICAL ASPECTS EPIDEMIOLOGY AND PATHOLOGY OF THE RICKETTSIAL DISEASES

I NONEXANTHEMATIC RICKETTSIOSES

1 "Q" FEVER

Synonyms—Australian "Q" fever American "Q" fever, Nine Mile fever, pneumonitis diaporica burnetiosis, Queensland fever

Definition

"Q" fever is a rickettsiosis caused by *R burneti* and its variant *R diaporica*

General Considerations

The term "Q" fever is derived from the region of Queensland, Australia, where the disease was originally observed The term could advantageously be replaced by the name "burnetiosis " as proposed by Macchiavello (1945) * Both "Q" fever and trench fever are among those rickettsioses which are non exanthematic or which exhibit only a transitory exanthem "Q" fever is differentiated clinically from trench fever by its lack of recurrent characteristics

The Australian and the American varieties of "Q" fever are intimately related, the causative agent of each disease having the same antigenic constitution although varying in virulence The apparently different epidemiology of the two varieties does not depend on intrinsic peculiarities of the infectious agent but rather on differences in reservoirs and vectors and in the routes and methods of propagation of the infection The portal of entry of the virus is of preponderant importance in determining the modality of the clinical picture

For many years the disease was known only in Australia as a natural infection, and in the United States accidental infections occurred among laboratory workers In 1946, the disease appeared in Amarillo Texas, in cattle handlers and showed the characteristics of a spontaneous infection

On the other hand 8 outbreaks of "Q" fever were observed among the allied troops in Italy, Greece, and Corsica during 1944 and 1945 Five of these were thoroughly studied and in 3 *R burneti* was recovered in laboratory animals A laboratory outbreak at Fort Bragg, attendant upon the manipulation of infected chick embryos, was similar to outbreaks seen in the

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related to a former attack of typhus and with vaccination against Rocky Mountain spotted fever The "X" strain of *R diaporica* was isolated from the blood

In the 15 cases described by Hornibrook and Nelson (1940), the disease was characterized by a sharp onset but was mild, a few cases resembling coryza and others having headache, chills, fever, malaise, generalized diffuse pains, and rarely nausea, vomiting and a nonproductive cough During the course of the disease half of the patients had retrosternal and thoracic pain All had insomnia Physical signs were practically absent, except for slight pulmonary dullness, a small increase in the respiratory sounds, of a broncho vesicular nature, and heavy crepitus over the area where the x ray showed the presence of pneumonitis The pulse was full but with bradycardia in relation to the temperature All laboratory tests were negative, including those on blood, urine, sputum, cerebrospinal fluid, etc

The soft infiltrative lesion, single or multiple, and of a density not uniform as in lobar pneumonia, resembled on the x ray plate a patchy broncho pneumonia Pneumonitis occurred 5 times in the lower right pulmonary lobe, and in 2 patients more than one lobe was involved

In the outbreaks seen in Italy the disease had a sudden onset, with chills fever, sweating, general malaise, weakness, frontal headache, anorexia at times muscular aches, vague thoracic pains, at times pleural in nature, and diarrhea with abdominal cramps

Among the soldiers who became sick in the United States although they were infected in Italy there was a period of incubation not less than 13 days on the average In rather more than half of the cases the disease began gradually, in the rest, onset was sudden with a more acute beginning and more severe headache Many had a sensation of chilliness or frank chills muscular aches, and slight gastrointestinal and respiratory symptoms The average duration of the disease was 4 days but in 10 per cent of the cases it was 7 days Although febrile, the disease was benign in all

In the Fort Bragg laboratory outbreak, 14 of 16 patients had pneumonitis on x ray examination, and the average duration of the febrile period was from 7 to 10 days

Most of the Italian cases occurred in winter and spring

Complications

In 3 cases a severe meningismus was observed with no alterations in the spinal fluid

Mortality

A fatal termination of the disease is exceptional

Immunity

Convalescents, human or animal, develop immunity The presence of antibodies can be detected by laboratory methods (agglutination, comple

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In the first case of "Q" fever which occurred in the United States (Dyer, 1938), in the Montana Laboratory the epidemiology was not established with certainty In the following outbreak in Washington, D C, which occurred in the laboratories of the United States Public Health Service in 1940, Hornibrook and Nelson studied the 15 cases of pneumonitis which developed among the 153 employees of the National Institute of Health The source of infection was not established although direct transmission by arthropods was disproved, and the possibility of droplet infection appeared more likely In these cases, as in the first one the isolation of the rickettsia and the serologic reactions left no doubt as to the nature of the disease and its similarity with the Australian infection (Dyer, Topping and Bengtson)

Clinical Symptoms

There have been a sufficient number of observations at the present time to permit a general description of the clinical aspects of the disease In many of the cases described previously as having no pneumonitis despite the evident infection by the respiratory route it is possible that the pulmonary localization was not perceived Nevertheless while awaiting more complete studies it is desirable to describe the clinical pictures seen in various outbreaks independently

In Australia, Q fever was described by Derrick (1937) as an acute febrile disease of man of low mortality resembling an attenuated form of typhus and with an evolution of 7 to 24 days duration The beginning is sudden with fever rising to 40° C and, after marked daily remissions, ends in crisis generally at the end of 1 week Typical cases have headache malaise, anorexia conjunctival injection photophobia backache and pains in the extremities and bradycardia An exanthem was seen in only 1 of 9 cases The blood shows no changes and the Weil Felix reaction is always negative In certain cases the disease runs a more chronic course

In the case of Dyer (1938) which occurred in May of that year a probable incubation period of 10 to 16 days was suspected The sickness began with pains in the eyeballs tiredness and general malaise In the days following there were chills and slight fever for 4 or 5 days On about the fifth day these symptoms ceased and the patient had profuse sweating at midnight a crisis which was repeated on 4 consecutive nights Aside from certain dental and joint pains (fingers) the patient felt well had a normal appetite and slight constipation The pulse rate fluctuated between 72 and 90 The hemogram and urinalyses were normal except for slight indications of albumin in the urine and blood culture and serum agglutination tests for typhoid brucellosis, and tularemia were negative A Weil Felix reaction of 1 160 was

in the perivascular and pleural there are focal accumulations of carbon filled macrophages as well as lymphocytes and plasma cells Rarely large cells resembling the foreign body giant cell are seen in the exudate The spleen presents the picture of "acute splenic tumor" according to the description of Kneeland and Smetana

Summarizing the most important findings are

1 Nodular or confluent nodular hepatization with peribronchial or peribronchiolar localization

2 Alterations of the alveolar epithelium

3 Interstitial lymphocytic infiltration

4 Collapsed alveoli filled with polygonal epithelioid cells

5 The large blood vessels enveloped with a dense lymphocytic and at times monocytic sleeve

6 The pleura over the zone of hepatization shows stratified mesothelial proliferation and polynuclear neutrophilic infiltration

Since the end of World War II the publication of all the reports about the epidemics of so called "Balkan grippe" have added to our knowledge of "Q" fever This "grippe" was seen in the civilian population of Greece and in the armies of the United States England and Germany in both the Balkans and Italy and appeared as epidemic outbreaks of atypical pneumonia during 1944 and 1945 These outbreaks appeared to be different from influenza and Athens was suspected as being the source of the infection It was noteworthy that in an outbreak observed in Italy among a regiment of parachute troops the majority of cases occurred in a single company of the regiment also the outbreak was explosive with a case incidence of 30 per cent and there were no other associated respiratory diseases Caminopetros had isolated a strain of "Q" fever in Athens and had maintained it in guinea pigs for about a year without identifying it this being done subsequently by the Commission on Acute Respiratory Diseases In various epidemic outbreaks the cases were proved serologically *

Studies of Caminopetros (1948) showed that goats and sheep in the suburbs of Athens were infected and that the infection passed to the milk and was preserved by refrigeration Later investigations have shown that "Q" fever is endemic in Italy both in the north and south and in Corsica Returning troops gave origin to an outbreak in the United States in a bomber group in Virginia

Cheney and Geib (1946) proved the existence of "Q" fever in Panama

There is increasing interest in this disease in the United States Recent publications tell of the outbreak of 47 cases which occurred in February 1946 in Building No 5 of the National Institute of Health Thirteen cases had pneumonitis and 5 had bloody sputum The attenuated cases were more difficult to diagnose The Italian antigen proved useful in serologic studies Treatment was ineffective

*Editor's note (O F) Robbins et al (J Hyg 44 6 63 1946) described an explosive outbreak among troops in Italy suspected of being propagated by dust The transmission of Q fever by dried feces of naturally infested ticks on hides also must be considered especially in Australia

ment fixation protection tests) The appearance of antibodies may be late toward the end of the disease Immunologically all the strains of *R burneti* or *diaporica* so far isolated are equal differing however in virulence

Diagnosis

Diagnosis is based on the x ray detection of pneumonitis on isolation of the rickettsial agent in guinea pigs or mice and on serologic tests to show the presence of antibodies a method which also permits serologic investiga tion of groups

Differential Diagnosis

Differentiation must be made from all the pneumonitides or atypical pneumonias described as cited by Dyer (Bowen 1935 Allen 1936 1937 Bock 1938 Reimann 1938 Smiley 1939 Murray 1940 and especially Kneeland and Smetana and Longcope 1940) Pneumonitis caused by toxoplasmosis must also be considered (Pinkerton and Henderson 1941) At present isola tion of the causal agent is the most exact method of differentiation

Pathology

The preliminary studies of Burnet and Freeman (1937) on the micro scopic pathology of Q fever in experimentally infected mice have been amplified by the similar investigations of Lillie (1942) in guinea pigs of Findlay and Perrin and Bengtson (1942) in mice inoculated by the peritoneal or nasal route and by Lillie Perrin and Armstrong (1941) in monkeys *(Macaca mulatta)* and in man

In guinea pigs and mice the lesions depend largely on the route of inocu lation The two chief types of lesions are a focal perivascular lymphocytic ex udate and granulomas with giant cells having excentric nuclei The small pulmonary foci or nodules of hepatization present an alveolar exudate epithelioid cells and lymphocytic and monocytic interstitial infiltration and are very similar to although not identical with the foci of pneumonitis seen in man in which the alveolar exudate has much more abundant fibrin

Firm granular hepatization is found in man about as often as are foci of pneumonitis Congestion may occur in the rest of the lung and edema in 1 or more lobules The spleen is large with friable pulp The heart is dilated

On microscopic examination slides of the lung tissue correspond to the picture of pneumonitis described by Kneeland and Smetana (1940) In the zone of hepatization the alveoli bronchioles and part of the bronchi are oc cluded by compact fibrinocellular exudate The cells consist of lympho cytes plasma cells large mononuclears and erythrocytes At times pyknotic elongated nuclei fibroblasts and bits of desquamated alveolar epithelium are found In the denuded area the exudate appears to adhere to the alveolar wall Polynuclear neutrophiles are scarce or absent Interalveolar septa are scarcely thickened and present accumulations of lymphoid and plasma cells and large mononuclears The capillaries contain but little blood there is al ways some *degree of fibrosis In the peribronchial* connective tissue, as well as

cases occurred as well in Mesopotamia and in Egypt. It did not assume importar during World War II although a few cases were reported. Pechtel and Werner (19 and Peña Yanez (1940) cite cases.

Etiology

The specific cause of quintana fever has been much discussed, the infectious age has not been clearly established. It is known that the blood of those suffering from t disease is infectious for healthy men from a few hours *after the appearance of clin* symptoms until about 450 days later in the exceptional cases of such long duration a that infectiousness is permanent even in the intervals between febrile bouts.

The presence of *R. quintana* in lice fed on the sick, and its absence in healthy lic *its appearance in lice between the fifth and the eighth day after ingestion of infectio* blood and its progressive increase in the feces during the following days, the lack pathogenicity of the rickettsia for lice and the duration of the infection during the li of the louse, its nonhereditary character and the parallelism between infectiousness t *presence of virus and of the rickettsias in the lice like the parallelism between t* mechanism of infection of trench fever and exanthematic typhus fever (lice feces spre over the bites, abrasions of skin, or conjunctiva), elimination of the virus in urine (as murine typhus)—all suggest that *R. quintana* is quite possibly the specific agent of t *disease, although, as in other rickettsial diseases, it has not been demonstrated directly* infectious material of human origin, including blood. The negativity of the Weil-Fel reaction, the lack of pathologic findings, the lack of reaction in laboratory animals inoculat experimentally with the virus, and the lack of recent outbreaks all are factors which, tak *together, leave this problem without an immediate solution.*

Munk and da Rocha Lima and Sikora found *R. pediculi*—nonpathogenic and ind tinguishable from *R. quintana*—in lice fed on healthy individuals. The large number asymptomatic cases and the prolonged duration of the virus in convalescents or in chron cases, the existence of a certain apparent racial immunity in countries with much pediculos the prolonged infectiousness of the louse feces for 4 or more months after excretion, and th high resistance of the virus to external physical agents suggest the necessity of cautic in deciding against the identity of the two rickettsias. Even the different degree of virulen shown in each may have another explanation than those put forward by *the opponents* the theory of the rickettsial etiology of trench fever, which arguments may be summarize as follows: *R. quintana* is identical with *R. pediculi* and since the latter occurs in norm lice fed on normal individuals, the presence of the former in cases of trench fever lac etiologic significance, *another agent being the true cause of the disease.*

Epidemiology

From the foregoing many considerations can be involved on the ep demiology of this disease. It is worth while to recall that the louse is the onl important agent in the transmission of the disease, and the convalescent car rier, or the inapparent case, the principal reservoir. In exanthematic typhu fever the louse does not act as a reservoir because the rickettsial infection i fatal for it; in trench fever the louse is not affected by the virus and main tains it for the rest of its life. It follows that the louse is also an importan *reservoir of virus—a terminal reservoir*, since the infection is not hereditary Excreta of infected lice are the immediate source of human infection and blood of the sick is the source of the infection in lice.

The disease has the same general epidemiology as human exanthemati typhus—i.e., it is favored by war, famine, misery, crowding, cold, associatio of sick and well—by all the factors which favor lousiness. But the carrier

The detailed report of the outbreak in Amarillo, Texas, in 1946 (Topping et al, 1947), described 55 cases, with 2 deaths There were 136 employees in the 3 branches of the involved abattoirs

In August, 1946, Shepard reported 33 cases of " Q" fever among 81 employees in a Chicago packing house The average incubation period was 19 to 25 days

Huebner et al (1948) report 17 cases in Los Angeles County and 100 additional cases in southern California related to infection in cattle (10 to 20 per cent of the cows), from which 4 strains of *R burneti* were found in 4 different dairies Oliphant and Parker report 3 additional cases of laboratory infections in 1948 Huebner, Hottle, and Robinson (1948) tried out streptomycin in experimental infection of chick embryos with " Q" fever, with mediocre results

II THE RECURRENT RICKETTSIOSES

2 TRENCH FEVER

Synonyms —Wolhynian fever, quintana or five day fever, funftagefieber, pyrexia of unknown origin, Meuse fever, shin fever

Definition

An infectious febrile disease, of recurrent character, possibly caused by *R quintana (wolhynica)* and transmitted from man to man principally by the human louse (*Pediculus corporis* and *Pediculus v capitis*)

Characteristics

Recurrent pyrexia with an incubation period varying from 1 week to 1 month following which there supervenes a series of as many as 10 to 12 febrile paroxysms (average 4 to 6), with an individual duration of 20 to 30 hours exacerbations which are accompanied by chills fever, and sweating During the clinical course there are signs of grippe various pains splenomegaly changes in sensibility evanescent exanthematic eruptions, and moderate leucocytosis It is stated that the Weil Felix reaction is negative The course of the disease is prolonged convalescence is long and stormy and subsequent immunity is transitory Mortality is nil

Incidence and Geographic Distribution

Trench fever was a disease peculiar to World War I It is possible that the epidemics of ' military sweating ' described during the previous century had the same etiology In 1915 it was observed in epidemic form in Poland and Volhynia being described by His and Werner in the German Army Graham Hunt, and Rankin and McNee, Brunt, and Henshaw (who named it trench fever) saw it on the Allied front The reports of the American and English commissions presided over by Strong and Byam, respectively, are the most valuable sources of information on the disease, and from these we have taken the data which follow Byam estimates that during 4 years there were about 800 000 cases among the Allied troops Strong believes that between one third and one fifth of all cases of sickness among the combatants were due to trench fever It occurred in epidemic form in Flanders France Poland, Galicia Bukovina Italy, Salonica, and Macedonia, and

3 RICKETTSIOSIS (RICKETTSIEMIA) WEIGLI

Mosing (1936) described an epidemic of a relapsing fever resembling trench fever among the workers in the laboratory of Professor Weigl who were in charge of feeding the lice used in the preparation of the vaccine of this investigator It is supposed that the infectious agent is a rickettsia called *R weigli* The disease is a septicemia which has no relation to exanthematic typhus The relationship of *R weigli* with *R quintana* and *R pediculi* has not been determined Some writers suggest that these are attenuated forms of trench fever

R weigli is differentiated from *R prowazeki* by its larger size extra cellularity and nonpathogenicity for lice

Other authors mention similar epidemic outbreaks under similar conditions but more exact studies on this matter are lacking

III PETECHIAL EXANTHEMATIC RICKETTSIOSES

4 EXANTHEMATIC TYPHUS

From the clinical point of view there are no differences between human typhus transmitted by lice and murine typhus transmitted by fleas A separate clinical description of the latter would duplicate, along general lines moderate cases of the former

On the other hand, the diseases are epidemiologically different and thus a separate description is required for each disease The differentiation of the virus based on experimental methods and laboratory tests, has been described in the general section

Synonyms—Of the 80 or more terms applied to classical exanthematic typhus and of the 50 used to designate murine typhus mention will be made only of those most frequently used

Murine Typh [illegible] Tolan
typhus of Bangalo [illegible]
of Saigon Cholon [illegible]
urban endemic of [illegible]
fever, flea typhus rat disease of Toowoomba, typhus minor, ancestral orchitis, [illegible]
fever, estival nondiffusible dermotyphus, sporadic typhus of Tonkin, Maxcy's disease
Hone's disease intermediate minor, murine, or endemic rickettsiosis

Classical Typhus—Human typhus, humanized, European, Old World, *historical*, *major*, epidemic, ataxic petechial fever, tabardillo, pintas, dermotyphus Brill s disease is a sporadic form of classical typhus and must not be confused with the endemic murine typhus of the southeastern United States

Definition

Typhus is a disease caused by *R prowazeki* or *R mooseri* and transmitted from man to man by the human louse and from rat to man by rat fleas, especially *Xenopsylla cheopis* It is not possible clinically to define the etiologic agent in the absence of epidemiologic or experimental data

and inapparent cases on the one hand and the volume of susceptible population and the degree of lousiness on the other are the factors which determine the epidemic or endemic evolution of the disease

Clinical Description

The incubation period is generally asymptomatic with prodromal symptoms (headache malaise restlessness insomnia) Toward the end of this period which on the average is 10 to 20 days in duration (6 to 7 days in cases of experimental infection caused by inoculation of the virus and 30 or more when the disease is transmitted by lice) the disease proper begins either suddenly or gradually

In grave cases the onset is abrupt the illness may begin when the individual is in the midst of his normal occupation and he may suffer an actual collapse Early dizziness may impede walking Onset is accompanied by chills and rarely by nausea and vomiting In a few hours the temperature reaches 39 5° or 40° C (103 104° F) The fever curve later assumes one of the following three types

1 Fever of about 3 days duration followed by recovery

2 Initial fever followed by an afebrile period and later with new exacerbations of temperature up to 12 or more (4 to 6 on the average) febrile recurrences which may show regular 5 to 7 day intervals of apyrexia or irregular periods of apyrexia

3 More or less continuous irregular fever in which an elevation of temperature is incorporated with the developments described below without any intervening period of normal temperature

On the second or third day or later and sometimes at the time of the second rise of fever there develops an evanescent exanthem in 5 per cent of cases according to Haagen more frequently according to others This lasts 6 to 48 hours and consists of a few to many (up to 200) pink spots of uniform size varying from 2 to 4 mm up to 6 to 8 mm in diameter appearing only on the chest back and abdomen and disappearing without residues These roseolas are macular rarely papular still more seldom vesicular and they always become pale on pressure

During the course of the disease the pulse is accelerated in proportion to the temperature alterations corresponding to paroxysmal tachycardia being noted and often especially in cases of slow evolution accentuated cardiac irregularities Systolic arterial pressure is high Respiration is normal unless there is an effort dyspnea

From the beginning of the disease intense headache is observed principally frontal at other times intracranial rarely parietal or occipital and there are retro orbital pains One of the characteristics of the disease is the generalized aching which after the first attack becomes localized in various sites especially in the lower extremities and changing in location from day to day These pains are osseous cartilaginous muscular tendinous articular etc and may be continuous or abrupt and transitory but in all cases they are more

occur but the persistence of the virus in the flea during the life of the latter inclines one to think that the usual situation is one of typhus endemicity among the rodents In man epidemiologic conditions cause what seems to be endemicity but in reality only sporadic cases of murine typhus occur in man Now if this typhus becomes epidemic it will resemble classical typhus and therefore does not merit separate consideration It must be especially noted that some writers such as Megaw, believe that humanization and epidemization of murine typhus probably does not occur, and that in those countries in which this phenomenon is described it is more likely that both types of typhus exist independently and simultaneously

Whatever the relation is between murine and classical typhus these can be described in relation to man in their most definite and peculiar epidemiologic manifestations

(a) **Murine Typhus** —Murine typhus in man as studied by Maxcy in the southern part of the United States has the following epidemiologic characteristics

1 Sporadic incidence especially in the fall

2 No relationship in the sense of contagion between cases

3 Absence of lice as vectors

4 Greater incidence in men than in women and children

5 Relationship of the cases to work places (such as food warehouses) which are heavily infested with rats and fleas

6 Possibility of proving the existence of typhus in rats and fleas by isolation of the virus or by special tests (serologic, etc)

7 Low specific human mortality

8 Clinical symptomatology commonly more benign than in louse borne typhus etc

We mentioned earlier the investigations which tend to concede certain value to the transmission of murine virus from rodents to man by the ingestion of food contaminated with the urine of typhus rats or by infection of the mucosa with rat excreta or with the feces of infected fleas

(b) ***Classical Typhus*** *—Petechial exanthematic typhus* transmitted by lice is maintained in endemic form in many countries such as Peru Ecuador Poland the Balkans etc and in these and in many others it has *frequently* assumed epidemic characteristics These epidemic periods have been well studied but not so the endemic

From the point of view of dynamic epidemiology endemic typhus *(classical) is characterized by a permanent equilibrium* existing in parasite vector and individual—susceptible or immune—in such form that the same number of cases of typhus are produced in the same period of time and within the same area being proportional to the density of the population

This endemic condition is seen in zones of heavy pediculus infestation of uniform social structure and of rudimentary economy, especially in densely

Epidemiology

We have already mentioned that the investigations of Maxcy, Mooser Zinsser and Castaneda and Dyer et al were successful in identifying and characterizing the typhus called 'Mexican' by Mooser a denomination which the author changed to 'murine' or 'endemic' in 1932 when its universal occurrence was made clear From the beginning Zinsser maintained that this differentiation based on the separation of this typhus from that transmitted by lice was incorrect since both can occur in epidemics or endemically Other writers thought that the designation *transmitted by fleas* would correspond more properly to the murine virus to differentiate it from the virus *transmitted by lice* but it soon became evident that among louse-infested populations murine typhus could assume the man louse man cycle that is to say could become humanized to use Zinsser's expression and that under these epidemic conditions it might or might not lose its characteristic property of producing the scrotal reaction (Mooser Varela and Pilz 1934 Castaneda 1939 Leon 1944) On the other hand Zwierz (1938) has isolated from rats nonorchitic strains The virus once humanized by many louse man passages would lose definitely its orchitic quality and its adaptation to rodents as would be the case of the virus of epidemic typhus observed in Europe The foregoing would signify that the sign of Mooser indicates that the typhus virus is still *in close relationship to rodents but that its absence does not include possibility* of a murine origin for the virus and that therefore the sign does not have pathognomonic value to define the intrinsic antigenic nature of the virus In this sense the complement fixation test is more exact for the reason that it is related to this antigenic composition But since epidemiologically the loss of the orchitic capacity indicates epidemization of the virus or in other words passage by the man louse cycle it must be considered that the differences between *R prowazeki* and *R mooseri* may depend more on the loss or acquisition of the qualities imposed by the changes in vector and host which indirectly would require the acceptance of a close relationship between both viruses This appears to have been proved serologically by Zinsser and Castañeda (1932) cytologically by Pinkerton (1936) and antigenically by Craigie et al (1946) and Topping et al (194?) The moment in which an epidemized murine virus ceases to be murine has not been defined by any specific test *Reversible* nonorchitic strains that is those which may reacquire orchitic properties and the so called *intermediate* strains signify an advanced progress along this road beyond which differentiation is not possible at the present time If the humanization of the virus signifies definitive changes toward what is understood by the term classical virus this differentiation would obviously be impossible

Therefore epidemiologically speaking in considering murine virus we must discuss it separately in rodents and in man and in relation with each of these both in the condition of endemicity as well as of epidemicity

But little or nothing is known about the endemic or epidemic occurrence of murine typhus among rodents From time to time epidemics may possibly

uniformity and interrelationship of the population and provokes small epidemic outbreaks, circumscribed in foci, and of capricious dispersion, which commonly are self limited

Epidemicity

A typhus epidemic may occur in a zone previously free from the disease or in a zone infected after a variable interepidemic period The extent of the epidemic will depend on numerous factors the susceptibility of the population, antihygienic factors and their distribution by social groups the degree and extension of louse infestation the season of the year and meteorologic conditions collective nutrition, crowding, etc

In any case the epidemic extends by the successive formation of new foci in increasing progression and of arbitrary distribution, although intrinsically the epidemic depends on the presence, distribution, and activity of the vector

Imported epidemics, and epidemic outbreaks in endemic zones usually begin with grave cases, epidemics which follow interepidemic latent periods have a large number of attenuated cases

The louse becomes infected by sucking the blood of the typhus cases but becomes infectious only in 3 to 8 or more days (up to 1 month in exceptional cases) of extrinsic incubation of the infection and remains infected during the rest of its life which in this circumstance, does not extend beyond 15 days The louse dies of starvation due to functional incapacity of the intestinal epithelium the parasitized cells of which burst and flake off In this period the feces of the louse are loaded with rickettsias Human infection does not take place through the bite of the insect, but when the feces from infected fleas are rubbed into the bite wound by scratching or by reaching the mucosal surfaces (conjunctiva) and even by the absorption through the respiratory tract of dried feces (laboratory infections) Starzyk (1938) demonstrated the long survival time of rickettsias in louse feces, Blanc and Balazard (1937) in flea feces Fedjin (1936) believed that louse feces could remain infectious up to 1 year Eyer, Przybylkiewicz, and Dillenberg suspected the occurrence of laboratory infections from dust containing the dried feces of lice The life of the louse is of variable duration during an epidemic Specimens taken from patients in the sixth day of the disease had an average survival time of 5 3 days at the height of the epidemic and of 11 8 days toward the end of the epidemic, 2 years later We have found lice alive 25 days after having been removed from patients when the lice are kept in a closed space without food (1939) They may, however, live under such conditions for 45 days or more The feces may remain infectious for years, this explains the annual reappearance of typhus in the so called "typhus houses" or old foci *R prowazeki* is not hereditary in the vector, and therefore the louse louse cycle does not exist unless one accepts the occurrence of infection by means of the feces of new generations of lice (Pchenichnof and Raikher, 1936) Neverthe less it must be emphasized that the important fundamental cycle is man louse man, within the classical mechanism, that is blood of a typhus case intestine of the louse feces bite wound typhus in a susceptible individual The same louse

populated homogeneous rural zones with little movement away from the limits of the area Change in one factor (immigration for example) may initiate an epidemic outbreak

Epidemic zones in their turn are characterized by a very variable curve of incidence of typhus and by a constant focal diffusion The epidemics may last for several years (with seasonal variations) and are followed by an inter epidemic pause They depend on a heavy louse infestation economic and social crises crowding together of uniform groups of population (shelters for unemployed asylums collective houses prisons etc) and changes in the makeup of the population (immigrants soldiers etc) and they develop by preference in dense and changing urban populations In epidemiologic dynamics there is a constant and persistent imbalance among rickettsia vector and man a disequilibrium which begins in susceptible human and social terrain progressively increasing and of a focal character augmenting to collective immunity as a resultant of the infection or until improvement in adverse social factors (exhaustion dislocations of human masses starvation crowding etc) or control measures limit it initiating a phase of endemicity or a phase of interepidemic quiescence or more rarely complete eradication of typhus The detailed study of the epidemiology of both types of cases is very interesting and the infectious agent the vector the source and reservoir of the infection the state of susceptibility or immunity of the individuals and the surrounding conditions all must be considered as is done in the following paragraphs

Endemicity

It appears that *R prowazeki* has less virulence and the infected louse a longer survival time during endemic periods The extensive infection in children explains adult immunity the low mortality of typhus (which is more benign in children) the apparent low incidence (infantile typhus resembles grippe often or develops without an exanthem) the endemic aspect and the local persistence The existence of human or animal reservoirs has not been proved the louse may be a temporary reservoir Woodsmen and children maintain the infection Nicolle originally and later many others among them Minkevitch (1930) and Korostobetz (1933) have pointed out this fact

Nicolle suspected the existence of inapparent carriers of typhus Ramsine (1929) found 13 per cent of healthy adults with a positive Weil Felix reaction in an epidemic near Belgrade Later Parykin (1930) Afanassiewa and Tretjak (1933) Ciuca et al Frmiloy et al (1935) Barykin et al (1930) Kraus and Castillo (1931) Veintemillas (1935) and others have proved that in zones of typhus endemicity 50 per cent or more of adults have serologically demonstrable immunity

Endemic phenomena develop preferentially in rural areas of uniform population and show few seasonal variations Cases have no apparent connection one with another The grouping together of people (at fairs religious celebrations group agricultural undertakings peregrinations etc) breaks the

Clinical Description

We have said that exanthematic typhus is a clinical entity A general clinical description may be made but it must be kept in mind that the clinical forms are quite variable ranging from grave hypertoxic cases to the so called inapparent or subclinical typhus that is to say cases with no symptoms Exanthematic typhus may be defined as a transmissible disease which in its typical form develops with high fever stupor or the ' typhus ' state and a maculopetechial exanthem There are recognized a period of incubation a period of frank illness with two phases the pre eruptive and the eruptive and a terminal period ending in death or convalescence

The **incubation period** is 10 to 12 days with extremes of 8 to 20 (9 to 10 days in human cases inoculated experimentally by Veintemillas Bolivia 1944) It is generally asymptomatic with indefinite prodromal symptoms at the end of the period of incubation (malaise lassitude general weakness anorexia character changes etc)

The **onset** is sharp with chills fever pains in the back and extremities vertigo nausea and above all a very intense headache a distinctive sign even in mild cases

During the **pre eruptive phase** the patient presents a characteristic facies bloated and congested there is injection of the conjunctivae (with bloody streaking) a thick coated tongue which the patient has difficulty in protruding asthenia which progresses to prostration a progressive intense headache nocturnal delirium dulling of the senses but no interference with consciousness a relaxed abdomen and a persistent constipation continuous elevation of temperature between 39° and 40° C rarely rising to 40 5° C or more the fever showing slight fluctuations and a variable morning remission and with a drop of 1° or 2° at the end of the pre eruptive phase

The **eruptive phase** begins on the fourth or fifth day and is characterized by the exanthem and stupor The exanthem develops all at once at first as pinkish pale macules of irregular and inexact outline varying in size between a pinhead and a lentil and disappearing on pressure In a few hours the number of spots increases and they become more or less confluent developing without any particular order on the abdomen back arms and thighs covering the extremities except for the elbows palms of the hands and soles of the feet and with no involvement of the face or scalp The face may show an exanthem (in 4 per cent of cases according to Megaw) although this occurrence at least in South America is exceptional On the other hand Megaw says that in 1 to 5 per cent of cases eruption may appear on the palms while Veintemillas observed this frequently in Bolivia In 24 hours the macules become dark red or wine colored and a day later they are definitely purpuric and petechial and do not disappear on pressure

The **stupor** or **typhus state** is the extreme prostration accompanied by indifference to external surroundings insomnia and persistent delirium accompanied by visions the delirium being mild or violent The patient lies inert passive in dorsal decubitus or on his side with knees flexed The face

may infect many persons Different cases of typhus are not equally infectious to the louse (Mooser 1945) Macchiavello (1938 1939) found the following percentage of infection in lice according to the gravity of the cases of typhus and the day of evolution of the disease serious cases—11 1 per cent on the third day 80 per cent on the tenth 50 per cent on the fifteenth less serious cases—40 per cent on the fourth day 20 per cent on the twelfth day, mild cases—50 per cent on the fifth day 25 per cent on the eighth In grave cases 50 1 per cent of lots of 6 lice each recovered during the course of the disease were positive in fecting guinea pigs in less serious cases 35 7 per cent and in light cases 17 8 per cent The so-called ambulatory or inapparent cases do not infect lice fed on them but in convalescents infected lice can be found during the course of the disease up to about 10 days after the fever drops (in exceptional cases up to 2 months) The transportation of infected lice by healthy individuals who later may or may not become ill with typhus is much less frequent than the transportation of infected lice by immunes (Macchiavello and Cifuentes 1942)

In practice the only source of infection for the louse is the blood of a typhus patient this infectiousness varying with the gravity of the case (during the entire course of the sickness in grave cases and possibly from the end of the incubation period for 9 days in ordinary cases and for 5 days in light cases) This infectiousness of the blood varies in any one patient even during a single day and is proportional to the gravity of the case always disappearing in 24 to a maximum of 36 hours after the drop in temperature

Regarding the conditions which affect receptivity of a population we mention that there are no natural immunes that children tolerate the infection better than adults that Indians and Negroes appear less susceptible than whites that typhus is more frequent in men than in women that the epidemic curve of typhus begins first in men that during epidemics a large number of inapparent cases exist side by side with clinical cases that the inapparent case plays no important role in disseminating the disease but on the other hand contributes to modifying the epidemic curve (Macchiavello 1938 1939 1942 1945)

With relation to social conditions typhus develops in foci and in large urban centers these predominate in unsanitary areas being limited to them With regard to climate typhus is more prevalent toward the end of winter and in spring since heat and excessive humidity influence the biology of the louse as well as affect general sanitary conditions (less clothing less crowding more cleanliness etc)

Although it is certain that nutrition plays a part in the evolution of epidemic typhus lack of vitamin C is not a factor as was suggested by Zinsser Castañeda and Sexstone Giroud and others although our investigations with Cifuentes and Ovalle (1939 1942 1945) indicate that vitamin C has an indirect effect on typhus by its capillary protective action It is possible that a low ingestion of albumin influences the gravity of the disease during periods of collective famine An analysis of the epidemic curve of typhus and its evolution will not be made here

2 That changes in conduction time involved especially a lengthening of the P R interval most often on the eighth to tenth day of illness the time interval at the beginning of convalescence being from 0 22 to 0 30 second or even 0 40 second instead of 0 12 to 0 16 second (normal) less frequently auriculo ventricular block of the Wenckebach type occurred



Fig 903—Human exanthematic (epidemic) typhus Section of skin from the trunk with typical exanthematic petechiae (Courtesy of I Herzog University of Concepción Chile reproduced from *Anat e Histologia patol de las lesiones org de T fo Exant etc IX Re ort of the Argent e Society of Reg o al Pathology* Mendoza, 1935 pp 5 4 600)



Fig 904—Human exanthematic (epidemic) typhus Nodular perivascular exanthematic infiltrations predominantly leucocytes in the reticular and subcutaneous *strata*. Oxydase stain (X41) (Courtesy of I Herzog University of Concepción Chile)

3 *That the most important changes were those of the ventricular com* plex modifications in the Q wave associated with lesions in the ventricular septum being observed in 30 per cent of cases in 48 per cent thickening hooking and low voltage occurred reaching maximum intensity at the height of the disease in other cases they saw flattening or inversion of the T wave and when this was found in the 3 leads the prognosis was grave mortality being 40 per cent They showed that marked alterations in the T wave occur in 82 per cent of severe typhus cases *this having a diagnostic and prognostic* value in hypertoxic cases

is flushed and tense the mouth half opened the tongue dry and cracked (geographic tongue) the lips and gums covered with sordes Deafness is a frequent and at times intense symptom During this period cardiac renal pulmonary nervous or other involvement may be observed (these are separately described) and progressive wasting of the body tissues begins

Between the eighth and the ninth day clouding of the intelligence may be complete and from this moment nervous symptoms become accentuated and pulmonary and cardiac signs increase About the twelfth day the terminal period begins this ends in recovery or death In the former case the patient appears to show increased agitation but toward nightfall he feels better the temperature begins to decline by short lysis and convalescence is initiated with a crisis of sweating and polyuria and with the recovery overnight of consciousness intellectual faculties and appetite In the fatal cases there is seen at times a rise in temperature over the previous fever level, a state of "coma vigil" ensues in which the patient appears to be awake but nevertheless is unconscious the sphincters relax subsultus tendinum occurs likewise carphology collapse and death In other cases the temperature may fall to normal or below the general condition remains grave for 2 to 4 days and the patient dies in syncope in the midst of prolonged unconsciousness or delirium

All these enumerated symptoms develop during a cycle of 14 days on the average after which in those patients who recover the fever lessens and a long and stormy convalescence begins This may commence with hypothermia sinus bradycardia asthenia fatigue and at times nervous and other sequelae

Systemic Alterations or Complications

The so called complications of typhus are actually systemic alterations which depend essentially on greater or lesser involvement of the small blood vessels of each organ due to rickettsial infection But with these alterations true complications occur as follows

(1) SKIN

The eruption may develop early or late appearing between the third and seventh day The rash has a mulberry color at times it is hemorrhagic accompanied by hematuria hematemesis and melena

(2) HEART BLOOD VESSELS AND BLOOD

Acute myocarditis is manifested by cardiac softening ("dead leaf" of French authors) diminution of cardiac sounds alterations in rhythm cardiac gallop and fall in arterial blood pressure Some writers believe that this acute myocarditis complete or partial is accompanied by a process of coronary endocapillaritis or endarteritis which would explain the cardiac collapse syncope and sudden death (Garreton Silva Hervé and del Solar (1935) found the following on electrocardiographic examination

1 That alterations in rhythm varied from slight extrasystolic arrhythmia to grave auricular fibrillation

philes disappear gradually during the course o
lar form The lymphocytes are in inverse ra
leucocytes, with an absolute and relative incre
more at the end of the febrile periods Monocy
and sixteenth days to constitute 15 to 20 per
rule, plasma cells also appear Myelocytes va
numerous The sum of all these characteristics
of Schilling Platelets decrease in number duri
end of the febrile period *In experimental s*
(1926, 1939), and in a minute analysis of 238 hun
that the hematology of typhus requires further
tion all the factors involved, because the blood
large measure on vascular changes and on con
(alkalosis hypochloremia, hypoproteinemia, vol

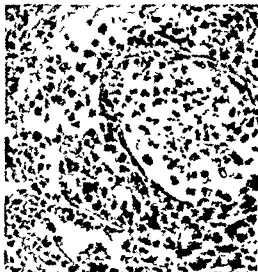


Fig 205—Human exanthematic (epidemic) typhus
with partial endothelial necrosis In the interior, leucocytes
Intense perivascular infiltration with hemorrhage Oxyda.
Herzog University of Concepción Chile)

Along with the pathologic changes caused n
small vessels, there are others which depend d
such as thromboarteritis, gangrene of the extre
tum Arteritis causes chorioretinitis, optic atro
changes in the sense organs Phlebitides are le
that these findings are only occasional, since typ

Luz (1942), Heller (1941), Fonseca (1942), and Woodward and Bland (1944) found similar or even more serious alterations of electrocardiography but they state that these are not of grave import, do not persist in convalescence and are not responsible for circulatory phenomena. In Chile Herzog and collaborators, especially Fernandez (1935), found that the most frequent histologic lesion is an acute focal interstitial disseminated myocarditis, diffuse myocarditis being less common, and that these lesions are not observed in typhus convalescents dying from other causes. Schittenhelm specifically denies the importance of myocarditis and other cardiac alterations in explaining circulatory changes. Fishberg (1940) found that in many infectious diseases peripheral circulatory insufficiency affects the heart without any organic lesion occurring. Harrell, Venning and Wolff (1944) and Woodward and Bland (1944) suggest that cardiac failure does not take place in typhus. The low arterial pressure has been suggested as being due to cardiac failure. Macchiavello and Cifuentes (1942) found that systolic pressure is not as low as stated by other authors, the fall in pressure is principally diastolic, and low differential pressure figures are noted until convalescence, but these changes in blood pressure are not of cardiac origin. At present all investigators agree that the great majority of symptoms usually considered as of a cardiac origin are in reality due to profound alterations in the endothelium of the small blood vessels, resulting in an increased permeability which causes manifold changes: edema, escape of water, salts and plasma into the tissues, diminution in blood volume, hypochloremia and hypoproteinemia, especially of the albumin fraction, which may drop to values one fifth or less than normal, low arterial pressure, relaxation of vascular tone, alkalosis, and increase of blood nitrogen (protein) to 90 or more milligrams per cent. Many cephalic, nervous and renal symptoms—but not all by any means— are due to this mechanism rather than to specific lesions. American writers point out the marked similarity between typhus and shock due to burns and suggest that the therapy should be the same, that is, above all the restoration of circulatory volume. Alessandri since 1934 has noted that the results of the parenteral injection of physiologic saline were at times disastrous and at times helpful. Only recently has this been explained as due to escape of albumin (along with salts and water) into the tissues, a phenomenon originating in the drop in osmotic pressure of the crystalloids (Harrell et al., Woodward and Bland 1944). We raised the question (1945) as to whether, in cases treated with convalescent serum, the apparent good results and the contradictory results were not due to the serum itself (homologous) and not to any specific antirickettsial effect.

There are some true changes in the blood, such as anemia and alterations in the leucocytes, but sudden variation in cell count is usually due to changes in hemoconcentration, quite variable in accordance with the dehydration or rehydration of the patient. Despite these fictitious alterations, the following changes may be established: a moderate leucocytosis subsequent to an initial phase of leucopenia, neutrophilia with marked regenerative shift, with 20 per cent or more of juvenile and stab forms. Leucocytosis and neutrophilia occur suddenly at the end of the disease when there is hyperpyrexia. The eosino-

of acute nephritis Schaffer (1944) found no uremia in the group he studied and concluded that this was seen only in cases complicated by glomerulonephritis in certain epidemics in cold climates In Chile Alessandri and collaborators especially Lozada Etcheverry and others since 1934 studied the chemical alterations in the blood in a large series of hospitalized patients Their results coincide with those obtained by all authors who consider that the essential pathologic physiology of typhus depends on the changes resulting from capillary permeability (the *transmineralization* of Schaffer) with hypochloremia hypoproteinemia dehydration etc the azotemia being a consequence of hemoconcentration faulty nitrogen assimilation diminished ingestion of fluids and of protein and only rarely due to a true renal lesion when this occurs it is due more to circulatory disturbances than to the infection Cafarena (1936) in autopsying 40 typhus cases found acute diffuse glomerulonephritis in 67 5 per cent combined with interstitial nephritis and acute focal interstitial nephritis in 22 5 per cent none of these findings being specific for typhus In 50 per cent of the cases there were hyperemia and leucocytosis of the interlobular capillaries not found in ordinary glomerulonephritis

(4) NERVOUS SYSTEM DISTURBANCES

Nervous system disturbances are common in typhus and usually develop during the second week which period is sometimes called the *nervous phase* From the time of Murchison Trousseau Gueneau de Mussy Cantacuzene etc the following groups have been described

(a) **Psychic Disturbances** —Acute psychomotor delirium (acute infectious mental confusion infectious oneiric delirium) generalized or systematized (with somnambulism or automatism) or depressive (suicidal) or with special tendencies (reduplication of the personality) also an absolute amnesia may remain during convalescence In fatal cases there occurs acute terminal delirium

(b) **Meningeal Reactions** —Meningotyphus

(c) **Cephalic Localizations** —Localized endarteritis or infectious encephalitis hemiplegias monoplegias jacksonian crises etc

(d) **Bulbopontine Localizations** —Tachycardia polypnea collapse labioglosso laryngeal paralysis frequent in the second week and of fatal prognosis ocular paralyses facial paralysis permanent deafness etc dysarthria disturbances in swallowing etc

(e) **Spinal Cord Localizations** —Generally appear late provoking vesical paralysis urinary retention and relaxation of the anal sphincter

(f) **Extrapyramidal Disturbances** —Resemble those of epidemic encephalitis with diplopia myoclonia crises of hiccup contractures pseudoparkinsonian tremors etc

(g) **Peripheral Neuritis** —Of the brachial plexus popliteal nerve sciatic nerve etc

(h) **Involvement of Vegetative Nervous System** —Asthenia rapid fatigue hypotension malnutrition muscular emaciation and other findings

and the French school in general, with which in some degree Yeomans et al (1945) are in agreement, attribute great importance to hyperazotemia as a cause of many symptoms of the disease, including the ataxo-adynamic syndrome, crises of Jacksonian epilepsy, epileptiform convulsions, intractable



Fig. [illegible]06.—Human exanthematic (epidemic) typhus. Focal exanthematic myocarditis. Typical perivascular nodule with lymphocytes, histiocytes, plasma cells and polymorphonuclear leucocytes. (×270.) (Courtesy of [illegible] Herzog, University of Concepción, Chile.)

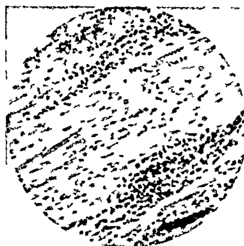


Fig. [illegible]07.—Human exanthematic (epidemic) typhus. Focal perivascular exanthematic myocarditis and [illegible] or oval forms. (×1[illegible]0.) (Courtesy of [illegible] Herzog, University of Concepción, Chile.)

vomiting, stupor and "coma vigil," persistent hiccup, myoclonia, miosis, Cheyne-Stokes respiration, coma and death. Wolbach et al (1922) specifically state that in their series there were no urinary alterations indicative

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(g) **Peripheral Neuritis**—Of the brachial plexus popliteal nerve sciatic nerve etc

(h) **Involvement of Vegetative Nervous System**—*Asthenia* rapid fatigue hypotension malnutrition muscular emaciation and other findings

It has recently been reported that uremia is an important cause of these disturbances This may be true in the terminal period of the disease in which azotemia is an important contributing cause but once again we may say that



Fig 208—Human exanthematic (epidemic) typhus Acute diffuse exanthematic ganglionitis of the nodose ganglion of the vagus nerve Oxydase stain (X?8) (Courtesy of L. Herzog University of Concepción Chile)



Fig 209—Human exanthematic (epidemic) typhus Focal exanthematic perivascular neuritis of the vagus nerve Gross (X180) (Courtesy of L. Herzog University of Concepción Chile)

the nervous symptoms result from a double order of phenomena the localization of the infection in the nervous centers which are exposed to the powerful rickettsial toxin and the vascular alterations mentioned including the changes in the composition of the blood

(5) DISTURBANCES IN THE RESPIRATORY APPARATUS

Coryza and "grippe" are almost constant at the beginning of typhus there may be tracheobronchitis or laryngitis, with dysphonia and a painful cough with scant pulmonary signs Late bronchopneumonia is a frequent complication

(6) DIGESTIVE DISTURBANCES

Aside from the alteration in the tongue ("parrot" tongue) and lingual tremor with difficulty in protruding the organ, we mention only anorexia and repugnance for food constipation (although diarrhea may also occur in a fifth of the cases) and vomiting

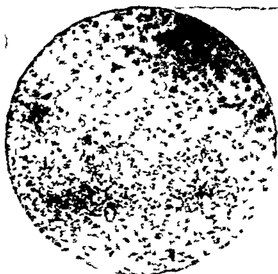


Fig 210—Acute diffuse interstitial nephritis Renal medulla. Human exanthematic (epidemic) typhus Oxydase stain. (×100) (Courtesy of L. Herzog University of Concepción Chile)

Frequency of Symptoms and Clinical Signs

In this respect it must be pointed out that the majority of studies of series of cases by different authors indicate selection of cases in one sense or another and therefore the figures relative to the frequency of symptoms do not correspond to the total number of typhus cases but rather to the total number studied

Clinical Forms

Typhus is so protean in its manifestations that a type description is always artificial Clinical forms are classified in accordance with their gravity and with the predominance of certain symptoms The following may be distinguished

1 Fulminating typhus *typhus siderans* typhus without exanthem rapidly fatal

2 Severe typhus *typhus gravis* with 3 clinical varieties the hypertoxic the ataxo adynamic and the hemorrhagic

It has recently been reported that uremia is an important cause of these disturbances. This may be true in the terminal period of the disease in which azotemia is an important contributing cause, but once again we may say that



Fig. 208. Human exanthematic (epidemic) typhus. Acute diffuse exanthematic ganglionitis of the nodose ganglion of the vagus nerve. Oxydase stain. (X 8.) (Courtesy of L. Herzog, University of Concepción, Chile.)



Fig. 209. Human exanthematic (epidemic) typhus. Focal exanthematic perivascular neuritis of the vagus nerve. Gross. (X180.) (Courtesy of L. Herzog, University of Concepcion, Chile.)

the nervous symptoms result from a double order of phenomena: the localization of the infection in the nervous centers which are exposed to the powerful rickettsial toxin, and the vascular alterations mentioned, including the changes in the composition of the blood.

orrhagic) and cardiovascular signs (mild carditis, arrhythmia) parallel the *nervous symptoms* Death occurs with a terminal hyperpyrexia between the eighth and tenth days, but there is another type, also common, in which the defervescence of the fever is followed by hypothermia and death In the ataxo adynamic forms, a violent delirium predominates with gesticulation and excessive talking, there is excessive movement of the musculature and extreme agitation all of which may persist until death or, between the tenth and twelfth day adynamia, profound stupor, and coma In the severe hemorrhagic type the eruption includes gingival hemorrhages, hematuria and melena, a fatal outcome being frequent

3 Clinical forms of *average gravity* do not require special description



Fig 213—Exanthematic perivascular infiltration of the renal cortex with partial necrosis of the endothelium of an arteriole Human exanthematic (epidemic) typhus (X 290) (Courtesy of E Herzog University of Concepción Chile)

4 *Mild typhus* includes all those cases with a short fever curve with the exanthem less intense and less extensive and with slight nervous signs and few complications The majority of cases of murine typhus and many of the classical typhus cases occurring in endemic zones correspond to this type Mild cases are very frequent even during epidemics and have great epidemiologic importance because they are controlled as are the more serious cases

One of the mild forms is called *abortive typhus*, which begins with the usual symptoms at times intense, but in which after 6 or 7 days there is a sharp crisis followed for not more than 2 or 3 days by only minor symptoms and finally, by a short convalescence

Another mild form is the *infantile typhus* in which nervous complications are rare mortality is low, and not infrequently the exanthem is absent or the eruption is atypical Infantile typhus commonly resembles grippe but often there is definite splenomegaly

The severe hypertoxic cases generally have a continuous high temperature (41° C or more) but not rarely cases occur in which the temperature is only slightly above normal. Nervous phenomena are marked (violent con-

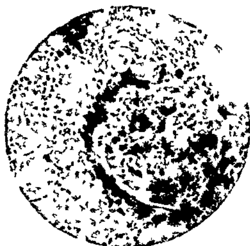


Fig 211—Acute glomerulonephritis with capsulitis Human exanthematic (epidemic) typhus Oxydase stain (X170) (Courtesy of I Herzog University of Concepción Chile)

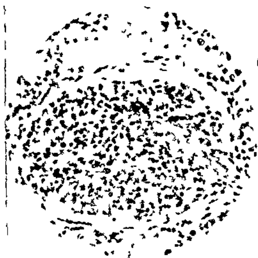


Fig 212—Intense acute glomerulitis with hyperemia of the capillary network and of the vascular pole Human exanthematic (epidemic) typhus (X340) (Courtesy of L Herzog University of Concepción Chile)

tinuous delirium fibrillary contractions subsultus tendinum carphology intense dyspnea without lung changes miosis of the pupils relaxation of the sphincters) Cutaneous phenomena (widespread eruption purpuric or hem-

Complications

Only the important complications will be mentioned parotiditis phlegmonous involvement of the lymph glands otitis mastoiditis abscess and edema of the glottis laryngotyphus secondary pneumopathies (bronchial pneumonias other pneumonias) purulent pleurisy association localizations gangrene etc In cases without complications the prompt recuperation of patients is remarkable except for pains in the legs and feet rapid pulse and some adynamia

Immunity

Typhus confers a lasting immunity on the patient although some authors mention the possibility of a second attack generally attenuated after several years Zinsser (1934) in studying Brill s disease concluded that this was a late recrudescence of typhus originally occurring in youth in immigrants from the Near East This theory presupposes latency of the infectious rickettsial agent in a state of premunition Loss of immunity would occur as a result of intercurrent diseases which diminish the biologic resistance of these individuals The author (1938 1945) expressed the opinion that the immunity of these inapparent cases seen in epidemic periods is relatively short as the epidemic curve of typhus appears to indicate The supposition that *man is a reservoir of classical rickettsial virus has not been directly proved* and the author does not know of any positive experiment in which lice fed on convalescents become infected 2 or 3 days after the definitive drop in temperature

Prognosis

The prognosis of typhus varies from epidemic to epidemic and is also variable in classical and murine typhus Mortality due to murine typhus may be less than 1 per cent On the other hand louse transmitted typhus may have a mortality of 22 per cent without marked annual variations The age of the patients also influences mortality

In Chile the mortality during childhood and youth is greater in rural areas than in the city of Santiago while the reverse is true during adult ages the total mortality for rural areas being less (15 1 per cent compared with 24 per cent 1939) which is a characteristic of rural typhus endemicity as stated in the section on epidemiology

The majority of typhus deaths occur between the ninth and twelfth day unless death is due to complications Clinical severity does not always indicate a fatal termination but those cases which begin with marked nervous disturbances with sustained hyperpyrexia or subnormal temperatures with leucocytosis of 20 000 or more and with a continued low titer in the Weil Felix reaction or those cases with bronchopneumonia pneumonia venous *thrombosis etc all have a poor prognosis*

Differential Diagnosis

The differential diagnosis of exanthematic typhus must be made with regard to the 2 varieties of typhus that is to say murine or classical as well as with regard to other diseases

The so called *ambulatory typhus (typhus ambulans)* is self explanatory, with a predominance of symptoms resembling grippe and with no eruption Headache is one of the important symptoms

5 *Inapparent typhus (typhus levissimus)* is usually without symptoms for which reason it is called asymptomatic subclinical and also serologic typhus since it is detected only by serologic reactions (agglutination complement fixation and others) It is important to note that the diagnosis should be



Fig 214 —Cerebral typhus nodule Patient S F Clinically nervous system form on autopsy typhus meningo encephalomyelitis Neotropical exanthematic typhus Minas Geraes Brazil (Photograph × 50) (Courtesy of Octavio de Magalhaes)

made only when increasing titers are found with these tests using fresh serum and frequent tests as well as proved antigens The inapparent case does not have the epidemiologic importance in our opinion that other investigators attribute to it

The foregoing classification has only a descriptive value since in individual cases the clinical gravity has little relation to mortality although the latter is greater in those groups with severe nervous or cutaneous symptoms

causes degenerative changes followed by proliferative reactions and infiltrative phenomena The aggregate of these focal lesions is the typhus nodule or Fraenkel's nodule

Lesions on the skin are more frequent but not exclusively so on a level with the rashes in the capillaries small arteries and veins and around the sweat secreting glands papillas and subpapillary plexus On the first day of the exanthem the endothelia are edematous sometimes to the extent of closing up the vascular lumen The endothelial cells show signs of mitosis stain slightly and occasionally are filled with rickettsias The connective tissue adjacent to the involved blood vessel contains many polymorphonuclear neutrophiles (Dawidowsky Wolbach et al) well brought out by the oxydase



Fig 215 —Experimental inoculation of guinea pig with virus of neotropical exanthematic typhus Scrotal reaction on the seventh day of the disease Minas Geraes Brazil. (Courtesy of Octavio de Magalhães)

reaction introduced by L Herzog (1935) Toward the fifth day of the disease there is evidence of the formation of mural thrombi on the walls of the blood vessels and at times occlusive fibrinous thrombi and the appearance of perivascular cells among them macrophages with clear cytoplasm polymorphonuclears and scavenger cells The typhus nodule thus formed is focal and progressive in character and during the succeeding days new nodules are formed in the larger vessels including those of the subcutaneous tissues Lesions of the intima are less frequent and those of the media exceptional In addition to the nodules there occurs a diffuse perivascular infiltration in the skin made up of mononuclear phagocytes lymphoid cells plasma and scavenger cells and many polymorphonuclear leucocytes as demonstrated by Versin Castellon using the oxydase reaction

Murine typhus may be suspected on epidemiologic grounds and confirmed by laboratory tests already mentioned

As for other diseases differentiation is difficult when epidemiologic data are lacking and the typhus case is sporadic The differential diagnosis must be made from typhoid fever relapsing fever measles meningococcic septicemia with eruption and human toxoplasmosis as described by Pinkerton and Henderson It was by means of a strict differential analysis of the clinical symptoms resembling those of typhus that we were able to make a diagnosis of the first case of toxoplasmosis proved during the life of the patient who in this instance recovered (Guayaquil 1942 1944)

Before the development of the eruption typhus may be confused with any infectious disease especially grippe At times it is very difficult to differentiate from other rickettsial diseases The basis for differentiation described in the first section of this chapter should be used in these cases

It may be said in general that serologic tests (Weil Felix specific agglutination of rickettsias complement fixation) especially when successive examinations show increasing antibody titers are the most useful diagnostic aids The different strains of Proteus OX allow investigations to be directed toward the rickettsial groups defined by Felix and Rhodes The possibility of residual and nonspecific Weil Felix reactions (anamnestic) including those in healthy individuals must be considered

Pathology

The macroscopic examination of the cadaver of a typhus case is not sufficient to identify the disease Cadaveric hypostasis or skin color may lessen the value of the eruption as a diagnostic point Congestion of the conjunctivae epithelium cerebrum and leptomeninges punctiform visceral hemorrhages dilatation of both cardiac ventricles splenic hypertrophy (inconstant) and the waxy degeneration of the abdominal muscles are not specific and the complications usually serve only to confuse the diagnosis

On the other hand microscopic histologic examination permits the detection of almost specific changes which are seen only in other rickettsioses such as in the spotted fevers as well as in typhus

The specific lesion of exanthematic typhus was mentioned by Popoff (1875) and described in the skin by Fraenkel (1914 1915) and in the brain by von Prowazek in 1914 The findings of these authors have been confirmed by Aschoff (1915) Benda (1015) Ceelen (1916) Bauer (1916) Jaffé (1918) G Herzog (1918) Spielmeyer (1919) Nicol (1919) Wolbach and Todd (1920) Wolbach Todd, and Palfrey (1922) Marinesco (1922) Morgenstern (1922) Golden (1945), Dawydowsky (1924) Wolbach (1948) Wohlwill (1944) and others In Chile Palacios Chavez and Avendano (1935) studied the pathology of experimental typhus and Herzog (1918) and Wolbach (1940 1948) human typhus pathology introducing new methods for study

The specific lesion is essentially (1) a lesion of the small blood vessels of the skin nervous system and some viscera which results from the localization of the infectious agent in the vascular endothelium and (2) the reaction produced in the neighboring tissues by its presence At the beginning it is seen that the intracellular localization of the rickettsias in the vascular endothelium

the focal blood vessels show thrombonecrotic lesions (G Herzog, Jarisch Dawidowsky), but Jaffé and Spielmeyer found neither serious necrosis nor proliferation of the cells of the intima or adventitia According to some (Wohlwill), if the terminal membrane which exists between the blood vessels and the parenchyma is intact, the proliferative lesion is mesenchymatous at the expense of adventitial elements and "Plasmazellen" Other authors believe that the true typhus nodules are formed by a proliferative glial reaction principally of the microglia (Kodama and Futaki, 1929), and rarely of macroglia (Wohlwill), or of the oligodendroglia in foci of the white matter Spielmeyer describes 4 types of nodules compact foci of 0 1 to 1 5 mm diameter, nodules occurring in rosettes in the cerebral and cerebella cortex, the so called



Fig 91 —Typical distribution of *Rickettsia prowazeki* in serosal cells Author's stain

Strauchartiges or *Gliastreuchwerk* of the molecular layer of the cerebellum and the *Gliastern* formed by 1 or 2 pericapillary layers of glial cells in the pons and medulla The participation of neuroglia and vascular elements in the formation of typhus nodules in the brain was well studied by von Prowazek Along with the circumscribed lesions are found diffuse infiltrations without selective topography The nodules develop in distinct epochs those of the medulla being the earliest They regress by disintegration or cellular migration and disappear without leaving any signs in about 2 months

The diffuse and focal lesions of the peripheral nerves have been studied by Morgenstern Marinesco Versine Wohlwill and others and are less important than the lesions of the sympathetic and parasympathetic systems studied by Abrikossoff (1923), Morgenstern (1922) Mogilnitzky (1924), Dawid

Hemorrhages around the capillaries and arterioles occur about the eighth day due to endothelial degeneration and rupture Regression of the thrombi takes place by means of organization and the disappearance of the nodules is brought about by the perinodular proliferation of fibroblasts around the eighteenth day with disappearance as well of the infiltrating cells through phagocytosis



Fig 216 — *R ckettsia mooser* in peritoneal serosal cells of rats irradiated with x rays Observe the filamentous and chain forms Author's stain.

The nervous system is surpassed only by the skin in the abundance of lesions These are also nodular with endothelial degeneration thrombi hemorrhages and perivascular infiltration of macrophages and polynuclear cells but without lymphocytes The preferred location is in the gray matter (mesencephalon pons floor of the fourth ventricle bulb molecular layer of the cerebellum the medulla etc) Lesions are more prevalent in the capillaries and precapillaries and not in the arterioles as in the skin In the nodules

hyperemia and an increase in cells from the beginning giving a positive oxydase reaction Golden (1945) found interstitial nephritis and hemoglobinuric nephrosis

Other alterations are found in the suprarenal capsules and in the gonads in the hematopoietic organs spleen and lymph glands and in the liver and other parenchymatous organs in general many of these are due to vascular changes or to increased activity of the reticuloendothelial system Golden believes that collapse in typhus cases is due to a focal necrosis and cytolysis of the suprarenals in addition to interstitial myocarditis and nervous system lesions

Wolbach and Todd (1920) and later with Palfrey (1922) deserve great credit for correlating these vascular endothelial lesions with the presence of rickettsia and of associating rickettsial activity with various perivascular manifestations



Fig 219 —Common grave form fatal case of neotropical exanthematic typhus Minas Geraes Brazil polymorphous exanthem principally petechial (Courtesy of Octavio Magalhães)

The modern investigations of Herzog and collaborators in the Institute of Pathology of the University of Concepcion Chile have been correlated with the new physiopathologic interpretation of the disease especially with reference to the much discussed participation of the heart and the kidneys They have also made it possible to establish an organic basis for the symptomatology dependent on the vegetative nervous system It is noteworthy that in all the pathologic studies of series of cases variations occur from one epidemic to another and it is therefore imprudent to make quantitative generalizations with regard to local findings in defining a standard pathology in a disease as multiform as is typhus

MURINE TYPHUS

There is little that can be stated with exactitude regarding the pathology of murine typhus since it is rarely fatal In the few cases studied it has been possible to establish that the pathology of the disease follows the same general lines outlined for exanthematic typhus although the specific lesions are less intense especially those of the nervous system

owsky (1924) and especially F. Herzog and Oyarzun who described the diffuse inflammatory processes and the focal nodules. The sympathetic ganglia (especially the superior cervical ganglion), the vagus (ganglion nodosum) and the intervertebral ganglia present a focal ganglionitis with discrete degeneration of the nervous parenchyma. These lesions appear early and the cellular degenerations and alterations are varied and intense.

The pathologic lesions of the peripheral vegetative nervous system, which according to Dawidowsky precede those of the central nervous system, will explain, according to Herzog, the vegetative symptoms observed in typhus patients.



Fig. 218. Exanthem in epidemic exanthematic typhus. Bolivian case. (Courtesy of Felix Veintemillas.)

Herzog and Rodriguez and Fernandez found alterations of 2 general types in the heart in 97.7 per cent of cases: the first, an interstitial inflammatory process (*interstitial myocarditis in small foci or diffuse*) *with a predominance of granulocytes* (55 per cent of cases) in the first or second week and an assortment of other cells and with no damage to the muscle fibers; the second, focal nodules like those already described. The lesions disappear without scarring. Golden (1945) found similar lesions.

In the kidney Herzog and Cafarena found no lesions in only 10 per cent of cases. In 67.5 per cent there occurred a diffuse acute glomerulonephritis and pure or combined interstitial nephritis, and in 22.5 per cent there was pure interstitial nephritis, focal or diffuse. In the former there occurs intense

serious cases between the years 1929 and 1937 The statistics of Patiño Camargo, in Colombia, for the zone of the Tobia and Negro rivers, and those of Montoya and Boshell, in Santander, *refer to infection in the municipal districts of Nimaima, Villeta* Quebradanegra, Utila, La Peña, Betulia, San Vicente, and Zapatoca, mentioning some 140 cases practically all fatal, between 1935 and 1942

In Mexico, statistics are very incomplete Bustamante and Varela (*1943, 1946*) found the disease in Sonora, Sinaloa, Durango, St Luis de Potosí, and Veracruz In India there is as yet no clear definition as to the status of this disease, although Topping et al recently proved its presence

Epidemiology

Spotted fever is essentially a rural disease which is transmitted accidentally to man during his journeyings through zones where infected ticks live (woodsmen, countrymen, tourists, etc) In some instances the ticks are transported to houses by dogs, giving rise to urban cases In Brazil, where the dog is a reservoir of the infection and where the vectors are habitual parasites of this animal, the disease has high domestic incidence as has been noted by Magalhaes, who also pointed out its characteristic suburban distribution in Minas Geraes

Because this disease is only accidental in relation to man, and because of the habits of the vectors, epidemic characteristics can rarely be assumed in districts with a very dense rural population and high tick incidence Infected zones generally show little tendency to spread The proportion of infected ticks, in spite of the hereditary transmission of the virus, remains more or less stable, according to various studies made in the United States, although it varies from one site to another (1 in 300 on an average) Climatic conditions favor transmission of the infection to man, the disease being more frequent during the period of the tick's activity (spring) and when man enters upon activities which put him in closer contact with ticks

In order for the tick to be able to transmit the infection, it is necessary for the virus to be "reactivated" *Nonvirulent, though immunizing, types have been described* (Spencer, 1929) Infection is maintained in the vector, so that a vertebrate reservoir is not essential Some ticks do not bite man, and therefore can transmit the infection only among their rodent hosts, for example, the *Haemaphysalis leporispalustris* of the rabbit, others, such as the argasid tick, attack man only exceptionally But both arthropods share their hosts with *D andersoni* and in this way can cooperate indirectly in the dissemination of the disease The principal ticks which transmit the infection to man are *D andersoni* in the western states of the United States, *D variabilis* in the eastern states, *Amblyomma americanum* in Texas and Oklahoma, *Amblyomma cajennense* in Brazil and Colombia and perhaps along the east coast of Mexico and *P sanguineus* in other sections of Mexico Infection takes place by means of the insect bite, but only after several hours of feeding of the tick on man (according to Parker, 1938, 8 hours or more) Infection may also occur by crushing the tick on the skin Moreira and Magalhaes (1935) and Dias and Martins (1937) have demonstrated, in Brazil, the important role played by dogs in domestic spread of the disease *Although numerous animal reservoirs of the infection exist,* among them opossums, wildcats, and wild rabbits, the disease occurs rarely in travelers, being more domestic, rural, or suburban In the United States, adult ticks are the principal transmitters, although among children nymphal ticks play a certain role In Brazil the disease is transmitted chiefly by nymphs of *A cajennense* (Magalhaes and Moreira), although *A striatum* has also been found spontaneously infected (Salles Gomes) Magalhaes and Moreira believe that *Cimex lectularius* is an important vector of the disease, which would explain the family *incidence of cases (as many as 12 in a single house)*

In the warm regions of Brazil, the incidence of the disease may be limited to the cooler, dry season Greater incidence has been found to occur in young adult males (Wilson and

IV EXANTHEMATIC MACULAR FEVERS

5 ROCKY MOUNTAIN SPOTTED FEVER

Synonyms—Blue disease, black disease, pinta fever, Bull fever, Rocky Mountain spotted fever, Western type, Eastern type, Minnesota variant (Zinsser), tick fever, Bitterroot spotted fever, specific infectious endarteritis (Wolbach), macular neoarctic macular rickettsioses (Amaral and Monteiro). Although in part differing epidemiologically, alike antigenically (or to date not distinguishable) are the spotted fevers described in Mexico, Brazil, Colombia and India under the following names: Sinaloa fever, Choix fever, exanthematic fever of São Paulo, São Paulo typhus, exanthematic neotropic typhus (Magalhaes), macular fever of São Paulo, typhus of Minas Geraes, Brazilian rickettsioses (pinto), macular neotropic rickettsioses, Brazilian typhus, Pisa disease (Meyer and Gomez), Tobia petechial fever, Tobia spotted fever of Colombia and Santander, Indian tick typhus, Megaw's disease, sporadic typhus-like disease of India, Kenya fever, and possibly also some forms of South African, North Queensland and Russian tick-borne fever.

Definition

Rocky Mountain spotted fever is an acute exanthematic macular febrile rickettsiosis caused by *Dermacentroxenus rickettsi* and transmitted by the bite of various ticks.

Characteristics

An exanthematic disease distinguished by macular exanthem, first petechial later, preceded and accompanied by fever, headache and various other aches, phenomena consequent to the specific endangiitis principally of the peripheral blood vessel.

Geographic Distribution

Before the recent knowledge of the enormous incidence of murine typhus, Rocky Mountain spotted fever was the most important rickettsial disease in the United States and still is from the point of view of its severity; this is also true in Brazil. Wolbach (1919) summarized the incidence in the United States from 1885, according to data collected in United States Public Health Reports (No 36, 1912). Cooley and the Montana State Board of Entomology mention for the years 1885-1912, 215 cases with 139 deaths and an annual mortality rate between 33.3 and 100 per cent; for 1913-1918 in Bitterroot Valley, 44 cases; and for other localities in Montana, 1915-1918, 58 cases (including one from Idaho). Summarizing various sources of information, Wolbach gives the following distribution of the different known cases between the years 1910 and 1918—Nevada, 81; Washington, 27; Colorado, 25; Montana, 135; Wyoming, 128; Oregon, 65; California, 39; Idaho, 1 909; Utah, 84; and South Dakota, 2. The cases reported by the United States Public Health Service between 19 8 and 1938 (in part), totaled according to Gordon 1943: New England and Middle Atlantic states, 65; Central Northeastern and Northwestern states, 137; South Atlantic states (Delaware, Maryland, District of Columbia, Virginia and West Virginia, North and South Carolina, Georgia and Florida), 951; Central Southeast (Kentucky, Tennessee and Alabama) and Central Southwest, 60; Mountain States (Montana, Idaho, Wyoming, Colorado, New Mexico, Arizona, Utah, Nevada), 2 044; Pacific (Washington, Oregon and California), 645. Gordon establishes that of the 2 190 cases reported between 1933 and 193 , 1 435 (65 per cent) were in the mountainous states and 601 (2 4 per cent) in the Pacific states.

In Brazil, for the region of São Paulo, Dias and Martins (1939) comment on a total of 88 cases between 1929 and 1933. Magalhaes in the district of Minas Geraes mentions 135

is seen The disappearance of the eruption begins with the decline (by lysis) of the fever although the petechiae persist for a long time especially if large subcutaneous hemorrhages have occurred Necrosis of the skin may also occur at various sites being most frequent in the scrotum prepuce fingers and ears A slight desquamation or even exfoliation of the skin persists during convalescence at times actual molds being formed There also occur areas of dead white epidermis and blotches corresponding to certain petechial lesions

In very grave cases the temperature may fall below normal 1 to 3 days before exitus death occurring generally between the tenth and fourteenth days except in fulminating cases when it occurs even earlier

In nonfatal cases the patient presents variable nervous and mental symptoms (restlessness insomnia hyperesthesia deafness delirium coma) after which convalescence begins with a drop in the temperature by lysis during the third week Gastrointestinal disturbances are not characteristic the urine shows a mild albumin reaction and a few granular cylindrical casts and is concentrated There is moderate anemia a slight leucocytosis and an increase in the percentage of large mononuclears Edema cyanosis and splenomegaly may occur Convalescence is relatively prolonged

Complications

The important complications are pneumonia phlebitis and hemorrhage the chief sequelae are deafness thromboangiitis obliterans nervous disturbances partial intestinal obstruction Second attacks of the disease are not rare and in mild cases immunity is not definite

Clinical Forms

Ambulatory abortive nervous and other forms have been described their importance rests in the diagnostic difficulties they present when they lack the eruptive phase and when their evolution is benign they are confounded with other rickettsioses especially with murine or epidemic typhus in areas where they co exist

Differential Diagnosis

In endemic zones diagnosis is simple and is made by a history of tick bite by the initial localization of the eruption etc In those countries where epidemic and murine typhus as well as spotted fever apparently occur such as India and Colombia diagnosis is extremely difficult and requires laboratory tests

The Weil Felix reaction is of value in suggesting the presence of a rickettsial disease but it is of slight differential value Virulence of strains isolated in animals is not necessarily related to virulence for man of these same strains

The differential diagnosis must include also other diseases presenting exanthemata such as the hemorrhagic purpuras cerebrospinal meningitis Colorado tick fever and others

Chowning 1902) but this seems to be due to other factors than a greater age group susceptibility All races appear to be equally susceptible but in Brazil the disease is more frequent among Mulattoes because of their greater relative proportion in infected areas There are fewer fatalities from the disease among children than among adults and mortality is highest among the aged Although the specific mortality is variable from one site to another, even in nearby areas the prognosis is always grave mortality being over 80 per cent in Brazil and Colombia In the United States the so called Western type commonly of high virulence has been contrasted with the Eastern type of more attenuated virulence Topping has demonstrated that this distinction is not valid both grave and benign cases being observed in any of the infected regions Moreover all the strains of spotted fever are alike immunologically the clinical pathologic and experimental differences seen being due to variations in virulence which at times are transitory

Clinical Description

There is no typical clinical picture which describes all cases of Rocky Mountain spotted fever since severe and mild variations are observed with such different aspects that they cannot be included in a common description Magalhaes in Brazil designated the disease neotropical exanthematic typhus not considering the term macular or spotted fever to be exact because the eruption as seen in that country is more of a pleomorphic type Cases are divided clinically into fulminating grave and ambulatory with hypertoxic nervous and other forms also described The same situation exists in the United States with the types called Western ' Eastern ' and 'Minnesota The following description is therefore a résumé of the findings which may be observed in the course of the disease

In the experiment of McCalla (1908) the incubation period was from 3 to 9 days The incubation period is usually considered to be between 3 and 14 days The disease has a sudden onset with chills headache generalized and joint pains and fever which rises rapidly to 40° C (104° F) or higher and remains high without morning remissions In more benign cases there may be an initial chill followed by several days of vague premonitory symptoms such as malaise anorexia etc In fulminating cases the temperature may reach 41° or 42° C (106° or 107° F) and remain high until death

During the height of the disease the patient may present the majority of symptoms of a grave typhus bloated face coated tongue with reddened edges and tip constipation photophobia a bronchial cough tachycardia dyspnea headache fever deafness etc

Usually on the third to the fifth day with extremes of 2 to 7 *days* the eruption appears first on the wrists ankles and back then on the forehead arms legs and chest and finally on the abdomen the face may also be involved as well as the palms of the hands soles of the feet and even the mucosa (enanthem) At first the exanthem is macular with spots 4 to 5 mm in diameter which disappear on pressure The macules become reddish or violaceous and toward the eighth to tenth day are frankly petechial The skin is smooth and shiny and its general appearance has been described as marble like or resembling the shell of a turkey egg At times a light subicteric tint

V BOUTONNEUSE RICKETTSIOSIS

6 BOUTONNEUSE FEVER

Synonyms —Eschar nodular fever, exanthematous fever, dothiendermie aigue, Marseilles fever summer dermotyphus, fever of the Mediterranean littoral, Kenya fever, Olmer's disease disease of Conor and Bruch, etc

Definition

Boutonneuse fever is an acute, febrile, papular exanthematic rickettsiosis caused by *R conori* and transmitted by *Rhipicephalus sanguineus*, the brown dog tick

Geographic Distribution

Prior to its description by Conor and Bruch (1910), the disease was known along the Mediterranean coast and in the Black Sea area It is endemic in these regions, especially in Italy, *Greece, Spain, Tunis, France and Portugal A small epidemic outbreak of 34* cases has been reported from Constanza, Romania In Kenya, Roberts and Tonking (1933) *described the disease as a local fever, later recognizing its true relationship to boutonneuse fever of the Mediterranean*

Epidemiology

Rhipicephalus sanguineus being an ectoparasite of the dog, most of the epidemiologic characteristics of the disease are conditioned by this fact The dog is the reservoir of the infection Human susceptibility appears to be generalized, and there is no preference for certain age groups The virus is hereditary in the tick, and the disease has greater prevalence in summer

Relationship to Spotted Fever

Badger (1933) and Hass and Pinkerton (1936) showed the antigenic relationship between boutonneuse fever and Rocky Mountain spotted fever *R conori* should be considered to be a subspecies of *Dermacentroxenus ricketts* from which it is differentiated by the infrequency of intranuclear localization of the former in the typical form of the microorganism A cross immunity exists betwen the two, and it is remarkable that vaccination against spotted fever does not protect against boutonneuse fever (Parker)

Clinical Description

The disease resembles closely both epidemic typhus and erythema multiforme Onset is sudden with chills and fever to 40° C (104° F), there are generalized aches and malaise, constipation or rarely diarrhea At the site of the tick bite a black macule, the *tache noire* of Pieri and Brugeas (1925), appears, a papular lesion resembling that seen in scrub typhus and which later develops into an indurated "button," nodose and painless, of blackish color and which ulcerates in the center and is accompanied by glandular swellings in the lymphatics which drain its site This *black escharo nodular* lesion is not seen in the Rocky Mountain spotted fever of the United States and only exceptionally is it seen in Brazil It appears in benign cases, while in tsutsugamushi fever a similar lesion is seen only in serious cases and is lacking in the mild ones

Prognosis

Prognosis is always grave, in the United States the average mortality is 22 per cent, and in Brazil it is over 80 per cent

Variants

Megaw (1917) was the first to suspect the existence of the disease in India, reporting his own infection caused by a tick bite Later Boyd (1935), Heilig and Naidu (1942) these latter also with Topping (1943), and recently Napier (1946) have studied the typhus diseases of India and have proved that at least a portion are Rocky Mountain spotted fever The subject requires further investigation

In South Africa as previously mentioned the studies of Pijper et al reveal the existence of a disease called South Africa tick bite fever Although the infectious agent is of the same group as *D rickettsi (var pijperi)* and the vectors are ticks *(Haemaphysalis leachi* and others), its relationship to the spotted fever group has not yet been completely worked out The Brazilian, Colombian and Mexican forms of the disease are identical with the classical, varying only epidemiologically

Pathology

Macroscopically one finds petechiae, hemorrhages, and icterus, there is venous congestion and the blood is dark and fluid Histopathologic findings have been studied extensively by Wolbach, and more recently by Lillie (1941), who reviewed the cases in the literature Comparative studies of typhus, spotted fever, and tsutsugamushi fever have been published by Settle, Pinkerton, and Corbett (1945) and by Allen and Spitz (1945)

Pathologic findings are in general similar to those seen in classical typhus, but there are a few marked differences Ricketts mentioned increase in volume of the lymph glands, also outstanding is the splenomegaly and the extensive hemorrhages, and the necroses reflect the extension of the vascular lesions The splendid studies of Wolbach demonstrate that the most conspicuous lesions are the alterations which take place in the blood vessels, principally those of the skin, subcutaneous tissues, muscles, and testicles and adnexa lesions which resemble those of typhus but which differ in showing a more profound destruction of the inner layers and a lesser perivascular infiltration The rickettsias first cause the well known alterations in the endothelium and later in the smooth muscle of the vessel wall Endothelial proliferation, vascular necrosis, thrombosis, infarction, and hemorrhage are prominent and cause areas of necrosis in the skin and subcutaneous tissues The more serious the case, the less time there is for development of these necroses before the death of the patient For the same reason cerebral lesions (typhus nodules) are seen only in prolonged or attenuated cases (Lillie, 1941) In addition, intranuclear and intracytoplasmic rickettsias in the endothelial cells and smooth muscle cells are pathognomonic of the disease Finally, Wolbach has pointed out that the experimental disease in the guinea pig duplicates point by point the clinical and pathologic findings of the disease in man

Definition

An acute exanthematic febrile disease caused by *R. orientalis* and transmitted to man by mite larvae

Characteristics

After an incubation period of 4 to 20 days a febrile phase ensues which lasts 2 to 3 weeks, accompanied by ulcerative lesions of the skin, with necrosis and with infarction of the lymph glands, generalized lymphadenitis, and a maculopapular eruption The fever ends by lysis, and the mortality is variable

Incidence and Geographic Distribution

The disease has been recognized in Japan for more than a thousand years and is endemic in the prefectures of Akita, Yamagata, and Niigata and along the banks of the Omono, Mogami, Shinano, Uonuma, Agano, and other rivers Two thousand seven hundred forty seven cases occurred in Niigata from 1903 to 1917; there were 111 cases in Yamagata from 1913 to 1917, in Akita, 1915 1917, 133 cases The annual incidence in Japan does not exceed 400 cases In Formosa scrub typhus is prevalent in the Kwarenko district

In 1921 Hatari identified the disease in Formosa, and Morishita (1942) listed the following incidence on the island of Formosa proper, 1923 1927, 403 cases with 52 deaths (mortality, 12 3 per cent), 1928 1932, 475 cases with 42 deaths (11 3 per cent mortality), 1933 1937, 144 cases with 15 deaths (9 6 per cent mortality); 1938, 22 cases with 6 deaths (27 3 per cent mortality) On the Fisherman's Islands there were 284 cases between 1932 and 1938, with 16 deaths, a mortality of 5 6 per cent

Later, the disease described in Sumatra by Schuffner and Wachsmuth (1908) as pseudo typhoid of Deli, and by Driel (1928) as mite fever, was identified with the disease observed in Malaya In the Malay States scrub or rural typhus had been identified by Lewthwaite and Savoor with tsutsugamushi fever, it being pointed out that the absence of an eschar in scrub typhus was not enough to warrant its classification as a separate entity. It is known that variations of scrub typhus exist in Indo China, China, Cambodia, Korea, the Philippines, Ceylon, the Bismarck Archipelago, New Guinea, Java, Australia, China, Burma, India, Siam, Annam, and in other countries, but statistics as to its true incidence do not exist

The identity of the local variants of scrub typhus is similar to that of the variants of Rocky Mountain spotted fever In 1945, Bengtson found a certain degree of serologic heterogenicity in strains of tsutsugamushi fever A degree of cross fixation, but not of identity, was observed in 37 human cases in Burma and the Philippines in 1946 by the use of different antigens, but definite serologic groups could not be defined Irons (1946) attempted to correlate the variations in severity seen in cases in 3 different areas with variations in virulence of the rickettsial strains isolated from a few cases and came to the conclusion that the most virulent strains were derived from the human outbreaks showing the highest mortality Our understanding of the occurrence of these variants of scrub typhus has increased with the study of epidemics among American troops stationed in Oceania These outbreaks show that scrub typhus has a wide endemic distribution, but it is not known why the disease is relatively less frequent among the indigenous populations of the endemic areas We have no exact data as yet on the number of cases of tsutsugamushi fever which occurred in the Allied troops in the Pacific Islands and in Asia, but an idea of its frequency can be obtained from the limited reports which serve as the basis for the clinical description which follows and which include the 70 cases of Ahlm and Lipshutz (1944) 225 (41 in British soldiers) seen by Klein (1945) in the Chin Hills of North Burma, 24 cases described by Philip and Kohls (1945) in New Guinea and the adjacent islands, 222 cases reported from the Philippines by Philip et al, 195 seen in New Guinea by Berry, Johnson, and Warshauer (1945), the 230 cases of Logue from the Southwest Pacific (1944), 626 cases among

On the third or fourth day of the disease the eruption appears, at first on the trunk, soon extending to the entire body, including face, palms, soles, and scalp At the beginning it is macular and disappears on pressure, being made up of lesions separated from each other by normal skin Later the macules develop into papules which later acquire a petechial aspect These papules vary in number and extent and may be nearly confluent

The course of the disease is about 12 days, and the patient does not appear to be very ill Mental and nervous symptoms and signs are usually absent The fever which at first shows light morning remissions of 1° to 2° C, begins to fluctuate more markedly and ends by lysis The exanthem disappears without desquamation

Complications and Prognosis

Complications are practically nil and there is usually no mortality In the epidemic of Constanza (Romania) there was a single fatality in the 34 cases

Differential Diagnosis

The usual low titer of the Weil Felix reaction and the absence of strong agglutinins in positive cases limits the value of this test especially when exanthematic typhus occurs in the same locality Differentiation from the other rickettsioses is made by the presence of the *tache noire*, the absence of lice the character of the exanthem and the laboratory tests outlined elsewhere in this chapter

Pathology

Pathology has not been studied in boutonneuse fever because the mortality rate is practically zero Histologic examination of the primary lesion shows a granulomatous process in which rickettsias have been described In typical lesions of the maculopapular exanthem there are structural changes consisting chiefly of edema of the vascular endothelium and in the case of petechial lesions, perivascular cellular infiltration, congestion, and hemorrhage (Olmer, 1933)

VI THE MACULOPAPULAR EXANTHEMATIC RICKETTSIOSES RURAL TYPHUS

(TSUTSUGAMUSHI FEVER, SCRUB TYPHUS)

Synonyms.—Tsutsugamushi byo, shimamuchi, akamuchi, shashitsu disease, Kedani fever,
Japane
cotters
tropical
Deli, river fever of Formosa classical mite fever of Schuffner, mite borne typhus Japanese type, Oriental rickettsiosis, Sumatra type, Malayan type of tropical rickettsiosis, Australian type of tropical rickettsiosis endemic glandular fever, tropical typhus K form, mite fever, mite fever of Sumatra, Indian mite typhus, etc

transmit it hereditarily through ovarian infection The new larval generation is therefore infectious transmitting to man possibly through the larval saliva Although numerous species of Trombicula are known only *T akamushi* and *T deliensis* (synonymous according to Womersley with *T fletcheri* and *T walchi* respectively) have been found naturally infected it is probable that other mites such as *Laelaps australiensis* also transmit the disease

The cause of the seasonal incidence in some areas is not clear In Japan the disease predominates from July to September in the summer season coincident with the larval activity of *T akamushi* There is year round incidence in Formosa On many of the Pacific islands where the disease had been unreported among the natives there were epidemic outbreaks among American troops

Local variations in mortality including that among soldiers may be related to virulence Japan has had a high mortality rate from scrub typhus between 30 and 60 per cent. In Formosa it averages about 12 per cent varying from 3 3 per cent in youths to nearly 50 per cent in the aged In the Fishermen s Islands mortality usually is about 0 6 per cent

Clinical Description

One learns from the publications mentioned that no one clinical description of scrub typhus will conform with all the cases The presence or absence of some symptom or physical sign may be not only a local characteristic but may be seen in patients in a single outbreak The description which follows is more a summary of the possible symptomatology than an attempt to describe any single case

The disease begins with the bite of the mite larva the patient not being aware of the bite or noting it only on touching the affected part Normally mite bites are irritating due to the salivary secretion but infected mites cause an initial papular lesion which later becomes ulcerated and necrosed due to the secretions of the arthropod and the secondary infection The lesion consists of a small wound in which the mite larva can be perceived with a hand lens The wound develops with necrosis in an area 4 to 6 mm in diameter the necrotic portion covered by a scab surrounded by a red or pink areola later an ulcer measuring 6 to 10 mm in diameter is formed Generally there is a single scab though at times two are found it is round and firm with a dark center without concomitant lymphangitis although there does occur involvement of the lymph glands which drain the site of the bite In some cases the lesion is a papule and resolves without ulceration Usually the ulcer begins to cicatrize at the end of the second week of illness

After an asymptomatic incubation period of 4 to 20 days (10 on the average) the sickness begins with headache fever malaise anorexia feelings of chilliness at times alternating with waves of heat sensation burning on urination cough and regional lymph gland swelling

The fever is remittent in type the temperature rising by successive daily steps during the first week to reach 39 5° to 40 5° C (103° to 105° F) During the second week a constant maximum level is maintained which later falls by lysis the fever curve lasting in all from 10 to 21 days rarely more Griffiths showed that in grave cases of 14 to 21 days duration the fever fell by lysis (in 70 per cent of the total cases) while in mild cases with short convalescence the fever falls by crisis (30 per cent of the total) after 11 to 16

Au tral an troops hosp tal zed in Ne Gu nea stu 1 el by W ll ams S ncla r and Jackson 931 analyzed l y Cr ff ths (1945) in Dutch Ne Gu ea 1 3 reported from the Ne Gu nea Arch pelago l y Bro n ng et al (1945) 1 000 ca es de cr l ed l y Tatter all an l Tattersall an l Iarry (1945) n Ind a the 35 ca es of Sang ter an l Kay (1945) the 49 cases of Anderson and W ng (1945) 615 treate l by De hmukh amo g Afr an combat troops n Burma 75 cases seen l y Men lell (1946) n Ne v Gu nea 80 in Cl ne e sol l ers descr bed by Agress and Evans (1946 64 cases of Ma lella an l Forrester (1945) of wl ch 40 ere among Ch nese and in a ld t on the cases of Sokolo and Carla d (1945) Ho ell (1945) Lev ne (1945) Ph l p et al (1946) Dame (1945) Andre (1945) Kohls et al (1945) etc It is poss ble that some of the cases reported are nclu led n more than one ser es

Epidemiology

The earl er ol ser at ons of Baelz (18 9) Hatar (1915 to 1919) I awam ra and Yamaguel (19 0 Nagayo 1916 a 1 1923) Wolff (1929 to 1932) Kou enaar Delbole Fletcher and Les lar An g te and mo e recently the reports of Heasl p (1941) n Austral a Mor h ta (1939 1942 in Formo a and others g e us an understan l ng of the cla cal ep dem olo y of tl e d e se tl e d fferent e dem c areas of tl e Pac fic Baelz as tl e first clearly to correl te tl e d ea e n Japan h the nundat ons of certa n r vers and he termed tl e d ease *Japanese floo l fe er* Later Hatar n Formosa pro e l that r ver flood ng as not e ent al for the occurrence of tl e s ckness and tl at there vere endem c zones h h ere not subject to undat on an l l h n o eover hanged n locat on from t me to t me

Then Mor sh ta ma le a on parative anal s of cond t ons on Formo a and on the Island Boko of the P she men s I lan ls and found tl at on Fo mosa ep dem cs occurred both in the lo lan ls and n the mounta nous zones up to 6 500 feet altitude Tl e d ea e as found n tl e fields river banks foot hill flatland oods and el e here being essent ally a d sease of feld workers tl at s those who wo k w th dome t c a mals woolcutters farmers Th s preference for erta n lal or cla es s related to tl e hab ts of the field workers and expla ns hy there s greater n len c in tl e age group o r 15 and un ler 50 an l also l y tl ere are mor cas s n men than n omen Sl gl tly le s than two th r ls of cases ere be een 15 and 35 years of age On the otl er hand on the P l ern en s Islands the d sea e is found n the v llages then l aroun l l uman l ab t t ons tl e only s tes here vegetat o adequa e for the levelopment of Tromt cula ex sts Tl e rest of tl e e land subje t to strong w nter mon oons wl l l lo up mu h salt water m ed ng tl e gro th of vegetat on favorable to tl e ve tor Moreover the host of the vecto *Rattus rat us ufes ens* tl e reservo r of tl e et olog c agent foun l spontaneously nfe te l by Yamam ya (1933 s e sent ally domestic All th s expla ns the dom est character of the d e se and the fact that all age groups are attacked but th a preponderance of cas s among ch ldren less than 15 years of age (70 per cent) and men and women show the same nc lence

Dur ng the o cupat on of the Pac fc slands by Amer can troops numerous ep dem cs of scrul typhus of var able exten we e observed Some of the invest gators ment oned above have attempted to correlate the character st cs of the terra n w th the relat ve in dence of ca es co clud ng n general that more cases were seen here forest vegetat on was mo t al un lant as n the areas m dway between tl e beach and the forest abandoned cocoanut gro es forests w th dense low grow ng vegetat on and all other s tes favorable to the e elop ent of Tro b cula the p es ce of h ch (when nfected) s the mmed ate cause of the d sea e Whether the infect on w ll be ep dem c or endem c depends on the num ber of nd duals exposed to these areas Some authors have stres ed that the true rese vo r of scrub t ph s s the ector tse f t l e ng unnecessary to seek a rodent or otl er reser o r to expla n the permanence of the d sease in endem c zones Mack e et al (1946 have proved nfect on n *T d l ens s* and hered tary transm ss on of the v rus

The percentage of nfect on of T omb cula larvae in the *yudokuchi* or nfected areas s qu te ar able and depends on cl aracter st cs of so l and vegetat on *such as kuna grass ta al b (Sa cl a um) kogan (Impe ator)* The larvae fall to tl e ground after the r s ngle bloo l meal Adult n tes not be ng hematopl agous do not transm t the d ease to man but

be brief or prolonged depending on individual circumstances and on the complications which ensue Mortality is variable

Mild cases may be diagnosed by the presence of the scar local or generalized lymphadenitis *fever and exanthem remembering* that one or more of these findings may not appear The Weil Felix reaction with Proteus OXK clarifies the diagnosis in doubtful cases

During the course of the disease *anemia is exceptional* The classic hemogram shows leucopenia with lymphocytosis of 40 to 80 per cent with the appearance of a type of lymphocytes which recalls those seen in infectious mononucleosis Recent series of cases show that leucopenia is not a constant finding and there may even be leucocytosis up to 20 000

The Weil Felix reaction generally develops late and is of value only when the titer increases It is said that it appears on the average in 9 days and reaches significant titers from the tenth to the sixteenth day In attenuated cases it is often absent Other laboratory findings are inconstant there being mentioned decrease in coagulation time of the blood delayed clot retraction time *prolonged bleeding time hypochloremia hypoproteinemia* increased sedimentation rate azotemia acidosis normal spinal fluid and albumin in the urine with a positive diazo reaction

In grave cases the patient may die between the twelfth and sixteenth day death being preceded by cyanosis edema filiform pulse low blood pressure cold extremities Cheyne Stokes respiration and coma Death is due to cardiac or respiratory failure Levine showed (1945) in a group of 130 convalescents from scrub typhus that electrocardiographic changes were minimal and that venous pressure circulation time and vital capacity were normal Exercise tolerance tests on the other hand revealed neurocirculatory asthenia with poor vascular tone as a consequence of the generalized vasculitis of the height of the disease Browning et al (1945) found minor electrocardiographic alterations in 14 per cent of 112 convalescents cosisting of low QRS voltage changes in the T wave and in the S T segment and in a few cases defective conductibility At the end of one month about half were normal again Howell (1945) found no abnormality electrocardiographically in 200 consecutive cases of scrub typhus nor did Berry et al find any serious cardiac abnormality

Many of the deaths that occur are due to respiratory involvement especially bronchopneumonia Among other complications of the disease are lobar pneumonia pleurisy pulmonary abscess bronchitis pulmonary infarct empyema laryngitis pharyngitis subconjunctival hemorrhage epistaxis hemoptysis hematemesis melena venous thrombosis and symmetrical gangrene rarely retrobulbar neuritis and various paralyses hallucinations delirium urinary retention sensory disturbances neuritis parotitis etc

Donegan (1946) found in 101 cases that ocular difficulties were transitory vascular and not due to nerve changes Dame (1945) found enlargement of the blind spot in 50 convalescents with contractions of the visual fields and scotomata in 98 per cent Seventy eight per cent of cases had deafness during

days of fever In the cases of Browning et al fever lasted fewer than 14 days in only 3 per cent of cases 14 to 21 days in 80 per cent and over 21 days up to 32 in 17 per cent Kohls et al reported that their mild cases had an average of 14 6 febrile days and the grave ones 18 days of fever

With the onset of fever there appears an intense conjunctival congestion with photophobia and at times subconjunctival hemorrhages Headache is intense and persistent the tongue is coated there is constipation or at times diarrhea and abdominal distention The patient begins to cough and this becomes accentuated and incessant There develop dyspnea and cyanosis generalized muscular aches especially in the lumbar region cutaneous hyperesthesia precordial pains a relative bradycardia (when compared with the fever) apathy clouding of the sensorium of varying degrees up to stupor mental confusion or even delirium There is persistent insomnia sweating crises deafness moderate splenomegaly at times enlargement of the liver One finds the local scab at the site of the bite and generalized lymphadenopathy this latter of great differential value By the tenth day of illness the patient is usually in a deplorable condition

Between the third and twelfth day more frequently between the fourth and seventh and usually by the sixth day a variable percentage of cases develop a more or less well defined maculopapular exanthem which in the majority is limited to the extremities and the trunk (and at times exclusively in one or the other location) Sometimes the face is involved and even the palms and soles At first the eruption is macular reddish or coffee colored disappearing on pressure later it persists on pressure Papules may not be very numerous although cases are cited which had an urticarial appearance Individual lesions vary in size from a pinhead to a diameter of 1 cm They may be isolated or grouped but rarely are confluent Some authors have observed that the eruption appears to be macular or papular on the face concentrated in the cheek areas later extending to the rest of the body Others describe a punctiform subcuticular eruption on the forearms and trunk appearing on the second day of fever The rash may last 1 or 2 days only but generally it is fully developed in 3 to 5 days and after an average duration of 6 days begins to fade leaving a slight pigmentation of the skin in some cases Others show no exanthem whatever and it does not develop in those undergoing a second attack of scrub typhus It is neither painful nor does it itch A day or so after the beginning of the exanthem one may find mucosal eruptions in the form of pin point reddish spots on the soft and hard palate and on the buccal mucosa The eruption has been compared to that of measles

Toward the end of the second week the disease is at its height The unconscious patient may have tachycardia dyspnea cyanosis delirium At this time respiratory and circulatory disturbances as well as nervous signs in grave cases reach their maximum The ulcer is very evident and from now on tends to heal and the exanthem begins to disappear The fever tends to diminish and symptoms in general lessen in intensity the adenopathy decreases and there is profuse sweating increased diuresis (3 days before the drop in fever according to Andrew) and frequent bowel movements Convalescence may

Pathology

In addition to the classical studies of Tanaka Hayashi and Kawamura we cite the findings of Williams et al (1944) (58 cases) McGovern in Australia (1945) (14 cases) Hicks (1945) (24 autopsies in Australia) Browning et al (1945) (6 autopsies) as well as the works of Settle Pinkerton and Corbett (1945) and of Allen and Spitz (1945) who make a comparative analysis of the pathologic characteristics of scrub typhus Rocky Mountain spotted fever and classical typhus

There is emaciation lymphadenopathy the scar (at times absent) enlargement of the liver and spleen edema dilatation of the right heart Lobar pneumonia may be found or ecchymoses and other evidence of diffuse hemorrhagic diathesis there is lack of coagulation of the blood in the vessels no thromboses extreme fluidity of the blood and pulmonary edema

Microscopic lesions include the following

1 Generalized edema and desquamation of the capillary endothelium diffuse interstitial infiltration with lymphocytes plasma cells monocytes histiocytes and at times polymorphonuclear leucocytes and parenchymatous cellular degeneration

2 Spotty circumscribed perivasculitis

3 The scar associated with secondary staphylococcic infection the thrombophlebitis and arteritis being septic in type Rickettsial reaction is seen in the veins remote from the central area and consists of mononuclear infiltration of the large vessels nonocclusive thrombosis and endothelial edema

4 In the skin lesion there is no necrosing arteritis but in the arterioles capillaries and veins lesions similar to the nodules of typhus are seen

5 Petechial hemorrhages in the serosa vessels mucosa of the renal pelvis testicles and lymphatic glands

6 Myocardial edema and epicardiac infiltration with inflammatory cells diffuse cellular myocardial infiltration rarely perivascular mononuclear infiltration of the intima of the large vessels with normal media and in the adventitia a perivascular collection of round cells in the vasa vasorum

7 Diffuse or focal hepatization of the lungs thickening due to edema congestion and cellular infiltration of the alveolar walls hemorrhages in the alveoli and their walls

8 *Cellular proliferation and vasculitis in the splenic pulp* edema and desquamation of the endothelial sinusoids lymph gland lesions are similar and also there are seen multinuclear giant cells resembling Dorothy Reed cells (Browning)

9 Hepatic congestion with mild fatty degeneration infiltration not perivascular

10 Edema and cloudy swelling of the kidneys at times endothelial desquamation of the glomerular capillaries diffuse cellular infiltration

11 In the central nervous system the lesions are vascular infiltrations edema gliosis and degeneration of the ganglion cells The cerebral nodules resemble those of typhus

the height of the disease, but only 11 per cent showed, during convalescence, slight alterations in the cochlear system, though 59 per cent had abnormal thermic response in the vestibular system

Diagnosis

In addition to the clinical picture already described, diagnosis is aided by the Weil Felix reaction, with Proteus OXK, specific complement fixation test with *R orientalis*, inoculation of susceptible laboratory animals, especially mice, and examination of the blood

Differential Diagnosis

Before the eruption appears differentiation must be made from the tropical pyrexias prevalent in the area especially malaria Once the exanthem is evident differential diagnosis must include the other rickettsioses occurring in the region During epidemics the identification of cases without eruption is somewhat easier Diagnosis of the disease depends on laboratory tests not within the province of the clinician

Prognosis

Mortality from scrub typhus or tsutsugamushi fever is variable, in Japan being from 30 to 60 per cent, in Formosa 12 per cent, in the Fishermen's Islands 5 6 per cent During World War II mortality varied greatly from one outbreak to another

The duration of the disease is decidedly correlated with the gravity of the case Andrew found that in serious cases the incubation period was 12 days, in less serious ones, from 12 to 17 days, and in subclinical cases, 18 days The length of the florid period, in serious cases was found by Griffiths to be 14 to 21 days, and in ordinary cases from 11 to 16 days In the series of Browning et al of 173 cases, 81 per cent had a convalescence lasting up to 2 months The shortest period of hospitalization was 2 weeks and the longest 16 weeks Of 27 cases, 75 per cent had returned to their normal occupations by 3 months and the remainder by 6 months Six patients died in 14 6 days on the average Death was more frequent at advanced ages Hayashi Nagayo Morishita and others found mortality to be very low in children and very high in adults, up to 50 per cent in the aged in Formosa and to 100 per cent in Japan The most frequent cause of invalidism during convalescence is neurocirculatory asthenia, a psychoneurosis may also develop, the individual believing himself to be a cardiac invalid Direct cause of death appears to be peripheral circulatory failure due to capillary lesions Increased capillary permeability may result in pulmonary edema, which is the cause of death in a certain number of cases, and which often is confused with the bronchopneumonia mentioned in the literature (Browning et al , 1945) Allen and Spitz do not believe that this mechanistic theory suffices, and they think that the peripheral circulatory collapse originates in suprarenal insufficiency

cose should be used *Chloride balance may be advantageously restored by the administration of ammonium chloride in doses up to 6 0 Gm daily* (Macchiavello 1938)

The author has tried nearly all the other nonspecific therapeutic measures recommended in the literature but without favorable results These are abscess fixation subcutaneous injection of aseptic pus and injection of leucocytes of sterile milk of vaccines etc

(b) **Chemotherapy**—We have tried the following drugs with negative results Neosalvarsan and Acetylarsan Lugol's solution Mercurochrome triple flavine Electrargol and various mercurials Magalhaes (1942) was also unsuccessful with colloidal copper sulfate Fuadin tartar emetic Septicemine Omnadin atropine orthophenol Neostibosan Bayer 205 Atabrine Sanochrysine etc Of little value also are Electromartiol Urotropin sodium salicylate Aurocolobiase etc Veintemillas (1943) recommended 1 to 2 per cent iodized tartar emetic Pinkerton and Hofgaarden (1942) had no results with Fuadin and atabrine

Macchiavello (1938 1939) and Macchiavello Cifuentes and Ovalle (1940 1945) exhaustively studied the effect of ascorbic acid on the typhus virus in vitro and in vivo There was no in vitro action on *R prowazeki* In animals and in typhus patients temperature is lowered during the administration of this substance and when given early in the disease by the intravenous route in daily doses of 1 0 Gm or more the general symptoms are improved especially those due to capillary alterations The same authors (*unpublished*) used vitamin B_1 in large doses in cases of anoxia in what may be considered emergency treatment this was used also in cases of arrhythmia and cardiac failure Pinkerton and Bessey (1939) showed that lack of riboflavin produced in rats loss of resistance to typhus It should be recalled however (Najjar et al 1944) that man can synthesize riboflavin in appreciable quantities in the gastrointestinal tract

As soon as the era of the sulfonamides began these drugs were used extensively Our results with sulfapyridine and sulfathiazole (1938) were unfavorable as were those reported by Kikuth 1939 (1940) Wohlrab (1942) and Scheller but we did not see in man the noxious effects of these drugs which were reported in guinea pigs with experimental murine typhus and spotted fever by Topping (1939) observations corroborated by Pinkerton and Hofgaarden (1942) Durand and Balozet (1941) Steinhaus (1943) etc On the other hand we noted a decrease in complications also reported by Monk (1942) and by Harmsen and Siegler (1944) Today the sulfonamides have been discarded in the treatment of rickettsial diseases except in pulmonary or *other similar complications which respond to this therapy*

Peterson reports beneficial results experimentally with a preparation called Forbisen and with toluidine blue (1944) Andrewes King van den Ende and Walker (1944) tried out more than 100 drugs finding activity in those designated V 147 and V 186 (p sulfonamidobenzamidine hydrochloride and its amidoxime) but these were ineffective in human beings

12 Allen and Spitz believe that the vascular atony is possibly of su[illegible] renal origin and not due to structural changes in the vessels Many of reactions seen have allergic characteristics

Settle et al find the lesions of tsutsugamushi to consist in acute gene ized endangiitis vasculitis and perivasculitis similar to the changes in typ and in Rocky Mountain spotted fever from which they differ in the follow points in exhibiting a primary ulcer and local or general lymphadenitis producing a specific pericarditis pleuritis or peritonitis and interstitial pi monitis in causing more frequent involvement of the large arteries especi the aorta in showing less frequent vascular thrombosis and in the nonhem rhagic character of the cutaneous eruption In laboratory animals—the w rat and the guinea pig—another characteristic is the occurrence of a muc peritonitis with many serosal cells replete with rickettsias (whatever the ro of introduction of the virus) while cerebral nodules are found only in th animals inoculated subcutaneously

Variants

Until an analysis of the antigens of a sufficient number of strains of *orientalis* has been carried out it will not be possible to establish on a s basis whether or not the clinical varieties of scrub typhus correspond to st antigenic variations of the etiologic agent

TREATMENT AND PROPHYLAXIS OF THE RICKETTSIAL DISEASES

I THERAPEUTICS OF THE RICKETTSIAL DISEASES

The therapeutic measures against the various rickettsioses are (1) n specific therapy and (2) specific treatment

(1) Nonspecific Treatment

(a) **General Measures**—General measures are (1) *maintenance of patient in as good a general condition as possible* (attention to the diet hyd therapy care of the skin cleanliness of the body orifices especially the c cavity ice bags to the head maintenance of bowel evacuation control diuresis etc) and the *administration of palliative or symptomatic treatm* adequate for the correct functioning of the different organs and systems su as diuretics (lactose squill Theobromine) cardiac tonics (Digitaline Native intravenous ouabain camphor sparteine caffeine ice to the precordium et nerve sedatives and others depending on the indications of involvement malfunction of the various systems

The resemblance of the rickettsial diseases to shock indicates the de ability of restoring blood volume with glucose or glucose and saline solutio after blood protein content has been re established to its normal value by t use of blood serum or plasma Fluid intake of the patient should be aroun liters daily For patients with anuria or oliguria intravenous 50 per cent g

embryos of *R prowazeki* and *R mooseri* in a dosage of 5 mg per cent but of *R orientalis* in doses of only 35 mg per cent

Recently acridine compounds have also been tried out especially Mepacrine Nitroacridine 3582 and its arsenical salt known as Rutenol Holler et al obtained good results with these drugs in the treatment of epidemic typhus and trench fever Experimental confirmation was rendered by Smadel et al (1947) using *R prowazeki R mooseri R rickettsi* and *R orientalis* The mode of action of the acridinic compounds is different from that of PABA More studies of these drugs are needed

Streptomycin has some action on the growth of rickettsias in fertile eggs (Morgan et al 1947 Smadel et al 1947)

The best therapeutic results have been obtained with Chloromycetin an antibiotic obtained from a Streptomyces isolated from earth taken from a field near Caracas Venezuela and now produced in crystalline form (Ehrlich et al 1947) Maclean (1947) and Smadel and Jackson (1947) showed that Chloromycetin has a definite inhibitory action in fertile egg cultures on the rickettsias of classical and murine typhus spotted fever and scrub typhus It also is active against the etiologic agent of rickettsialpox the *R akari* Therapeutic effects against typhus have been demonstrated by Payne (1948) in Bolivia and by Smadel et al (1948) in Mexico It is equally effective against tsutsugamushi fever (Smadel et al 1948) The drug is administered orally using an initial dose of 4 Gm followed by 0 25 Gm every 2 hours In tsutsugamushi fever treatment for 24 hours or less usually suffices*

Smadel Woodward et al (1948) reported the successful treatment of 25 scrub typhus patients with Chloromycetin Characteristic clinical features of the disease were present in each case and from the blood of each could be recovered the specific rickettsia or a diagnosis accomplished by agglutination or complement fixation procedures All treated patients received initial doses of 50 mg Chloromycetin per kg of body weight followed by 0 2 to 0 3 Gm every two to four hours At first treatment was continued for at least 12 days following onset of symptoms with a total dosage of 8 to 15 5 Gm Duration of treatment was gradually reduced and the last 7 patients received a total of 6 Gm within a single 24 hour period

Dyes have been found effective experimentally but tryout on human beings has not been warranted (methylene blue Otto and Schafer 1936 Kikuth and Schilling 1944 toluidine blue Peterson 1944) activity against various rickettsias has been demonstrated

According to Ferro Luzzi and Ferro Luzzi (1947) aspirin greatly lowers the mortality and diminishes the complications of typhus although it only slightly shortens the course In a series of 94 patients they had only 1 death (with a mortality of 14 8 per cent in the control series) In a second series the mortality among 74 cases of typhus was 5 4 per cent (with the rate 10 7 per cent among the 112 control cases)

*Editor's note (O F) Aureomycin and Terramycin are also very effective

Penicillin has been applied to the treatment of rickettsioses Greiff Pinkerton and Moragues (1944) and Moragues Pinkerton and Greiff (1944) believed they saw a certain inhibitory effect on the growth of the rickettsia of murine typhus in egg culture and some results in the treatment of experimental murine typhus in mice Edmunds (1944) reported cure of a case of Rocky Mountain spotted fever treated with penicillin Magalhaes and Rocha (1944) in dealing with experimental infections in guinea pigs with São Paulo typhus found the drug effective when applied intraperitoneally in doses of 25 000 to 30 000 Oxford units per 24 hours Yeomans et al (1944) reported its use in 4 cases of typhus but drew no conclusions however they advise penicillin for those complications which respond to its action Fitzpatrick (1945) tried it without success in experimental infection of guinea pigs with Rocky Mountain spotted fever pointing out as do Hamre et al (1943) that it is toxic for these animals in high dosage Summarizing it appears that penicillin is not effective against rickettsias Steinhaus and Parker (1943) obtained negative results against the agent of Rocky Mountain spotted fever with tyrothricin

On the other hand p aminobenzoic acid (PABA) seems to be of first importance in the treatment of rickettsial diseases in which it has so far been tried and at the moment it is the treatment of choice Snyder Maier and Anderson (1942) were the first to use it against experimental typhus in mice obtaining 80 per cent survival as compared with 20 per cent in the controls Hamilton Plotz and Smadel (1943 1945) proved that it inhibited the growth of the typhus and spotted fever rickettsias in fertile egg cultures Yeomans Snyder Murray Ecke and Zarafonetis (1945) gave the drug in doses of 4 0 to 8 0 Gm initially followed by 2 0 Gm every 2 hours orally in 20 typhus patients and obtained surprising results Anigstein and Bader (1945 1946) proved the antirickettsial activity of PABA in experimental spotted fever and Rose Duane and Fischel believed they obtained equally good results in a human case Snyder and Zarafonetis (1945) and Murray Zarafonetis and Snyder (1945) found that it prevented a fatal outcome in gerbilles inoculated with the virus of tsutsugamushi fever Tierney (1946) in treating 18 cases of this disease with dosages sufficient to obtain a blood level of 30 to 60 mg per cent of PABA noted shortening of the duration of the disease especially of the duration of fever with diminution of symptoms among them lymphadenitis and a lowering in the number of complications and fatalities The drug is to be discontinued if patients show mental confusion or if the white cell count drops to 4 000 per cubic millimeter with less than 30 per cent of neutrophiles

P aminobenzoic acid does not act directly on the rickettsias, it is possible that it is effective through the inhibition of certain enzymes necessary for the cellular metabolism of the organisms

P aminobenzoic acid has been used successfully in murine typhus in about 40 cases (Smith 1946 Levy and Arnold 1946 Diaz Rivera et al 1946) the usual dosage being 2 Gm in 25 c c of 5 per cent sodium bicarbonate every 2 hours PABA should be given before the eighth day of the disease, the optimal dosage is not known experimentally, it inhibits the growth in chick

In conclusion there is outlined the following scheme for the management of cases proved or suspected of having one of the various rickettsial diseases

1 In cases seen during the incubation period (or in contacts exposed to grave cases of one of the rickettsial diseases transmissible from person to person) give from 5 to 20 c c of convalescent serum preferably concentrated or hyperimmune animal serum

(2) In cases seen at the beginning of the disease one may use p amino benzoic acid vitamin C ammonium chloride physiologic saline and hyperimmune animal serum

3 In grave cases with circulatory failure hypoproteinemia anoxia nervous symptoms oliguria etc use blood serum or plasma restore chloride balance by the oral or intravenous route give sufficient but not excessive amounts of fluid and administer vitamin C vitamin B_1 suprarenal extract and hypertonic glucose cardiac tonics are given only when necessary The first therapeutic aim should be to treat the vascular shock of the patient PABA and hyperimmune serum do not appear to be effective in late treatment of grave cases

4 Penicillin and sulfadiazine are used in the infectious complications when it can be expected that they will respond to these medications

5 In all cases careful nursing attention as well as a diet rich in proteins is essential and adequate laboratory control of the therapeutic measures should be instituted especially when we use drugs the activity of which depends upon the continual maintenance of a certain blood level of the drugs

II PROPHYLAXIS OF THE RICKETTSIAL DISEASES

Megaw s division of the typhus fevers into 2 groups the *demic* and the *zootic* has practical value which is appreciated when one confronts the problem of the prophylaxis of the rickettsioses since methods applicable to the control of classical typhus fever (for example an epidemic disease transmitted from person to person when lice are the vector) cannot be the same as methods used against most of the other rickettsial diseases which are for the most part endemic or sporadic in character Whereas the demic group requires procedures of control which affect the general population and the vector both as regards the sick persons as well as his contacts the zootic group requires methods which do not have the same amplitude and which at the most may be related to the exposed population or to the infected vectors having usually an individual rather than a general character

Prophylactic measures against the rickettsioses are of two general classes (1) those which destroy the infective agent indirectly by means of elimination of its vectors or reservoirs and (2) those which protect the individual against the infective agent Collective protection of the members of a community implies the operation of an official sanitary organization Methods at our disposal in carrying out this protection are either biologic especially sera and vaccines or nonbiologic such as insecticides rodenticides administrative and legal procedures etc

Forbisen " used by Peterson (1944) is 4 4 bis antipyrine Although theoretically riboflavin ought to be an effective therapeutic agent since its absence favors development of the disease in rats it has been found ineffective experimentally in mice

2 Specific Treatment

(a) **Convalescent Serum**—Lewascheff (1893) Legrain (1894) Detre and Bussiere Decourt and Sallard (1930) Felin and Frackmann (1933) Durand (1933) Veintemillas (1936) Ashenhov Pfeffer and Sauwerky (1943) Alwens and Frank (1943) and Castano Castillo (1944) have reported some favorable results in the treatment of typhus with convalescent serum as has Fuhler with whole blood (1944) Chilean physicians who have used serum *extensively in recent epidemics agree with Levaditi and Lepine (1938) that* it is useless In 1939 we tried serum treatment again using convalescent serum concentrated by a simple technic (Macchiavello 1943) Our experimental results (Ovalle 1939) were very favorable in guinea pig typhus but in human typhus there was no therapeutic effect though the procedure was very effective in preventing the disease Perhaps the same holds true for the other disease of this group

(b) **Serum of Hyperimmunized Animals**—Nicolle in Bizert treated typhus cases with immune serum of donkeys with doubtful results The antityphus serum of Zinsser and Castaneda (1934) prepared in horses was shown to have real preventive value and was used by Varela and Bosque Pichardo (1934) and by Bustamante Varela and Rios Negri (1935) in the control of epidemics of murine typhus in Mexico and by Macchiavello (1937) *in Chile in the control of epidemics of classical typhus fever A medical com*mission appointed by the Mexican Department of Health and Macchiavello (1938) concluded that this serum known as the Harvard serum had a certain beneficial effect in the early treatment of both types of typhus Wolman (1944) in Abyssinia used an antityphus serum prepared in horses with living rickettsias from lice intestines Dosages of 20 c c given twice on the first day and 20 c c daily for 3 more days reduced the mortality to 3 6 per cent in controls it was 10 9 per cent Topping (1941) Kuretchin van der Scheer and Wyckoff 1943 and Fitzpatrick (1945) found that hyperimmune rabbit serum was effective in preventing spotted fever and had some therapeutic value in human cases

In 1937 Burnet and Freeman demonstrated the presence of protective antibodies in the sera of convalescents from Q fever (experimentally) Bengtson (1941) developed a hyperimmune rabbit serum capable of neutralizing up to 500 000 minimal infecting doses per cubic centimeter in guinea pigs We do not know whether this preparation has been used in the therapy of the rickettsioses It should be mentioned that the protective or curative power of a serum does not parallel its Weil Felix titer but rather its virus neutralizing power

rickettsias (which have been attenuated or killed) is not sufficient, in our opinion, to warrant calling these products *vaccines*, a term which should be reserved for immunizing substances of vaccinial nature which have well defined methods of preparation and which have been developed with the objective of effective human application, even though this objective may not yet have been realized On this basis the following vaccines are outlined

A. "Q" Fever

I Vaccine of Bengtson (1941) —

Prepared with *R diaporica* using (1) spleen and liver of infected mice and (2) method of Cox. It is a killed vaccine, carefully standardized, and has shown good results experimentally It should be used to protect laboratory workers who handle "Q" fever virus and *workers in abattoirs dealing with infected animals*

B Exanthematic Typhus

I. Vaccines Prepared With Killed Organisms —

(a) Vaccines Prepared With Organisms From Arthropods —

1 Vaccine of da Rocha Lima (1918) First prepared with a triturate of lice, later with lice intestines from insects fed on typhus cases

2 Vaccine of Weigl, 1929 (1933) Purified emulsion of intestines of lice experimentally infected by the anal route according to the method of Weigl (1920) Given in three doses, the original concentration of the total dosage is equivalent to 175 lice and 8,750 million rickettsias, the present concentration is equivalent to 90 or fewer lice Satisfactory results reported by Weigl (1933), Chodzko (1933), Mosing (1938), Herzig (1939) (in 120,000 vaccinated persons in Poland, 0 09 per cent developed typhus either during immunization or up to one year later), Anigstein (15 cases developed among 10,000 immunized medicosanitary personnel), Tobang and Lotsong (1934), and Rutten (1936) (among 200 Belgian missionarie [illegible] years, where before there were 4 or 5 cases [illegible] 1937) (after 13 980 vaccinations in Jawor [illegible] to 12), Mariani (1939) (*of 13,076 individuals vaccinated in Ethiopia, 8 developed typhus, 5 of whom* had not received the third dose of vaccine), Eyer, Przybylkiewicz, and Dillenberg (1940) (15 cases among personnel preparing vaccine), Eyer (1941) (good results in the medical service of the German army) Although of proved efficacy, this vaccine is very difficult to prepare on a large scale

3 Vaccine of Chrzanowski and Mosing (1933) Feces of lice are used, *phenolized* and the vaccine is prepared in the same manner as that produced in Weigl's laboratory

(b) Vaccines Prepared With Infected Organs From Experimentally Infected Animals or From Typhus Patients —

4 Vaccine of Handl *Prepared from* blood of human cases of typhus The blood is inactivated at 60° C or by chilling (42 hours in the refrigerator) Results are inconstant

5 Vaccine of Blanc (1915) Spleen and suprarenal capsule of guinea pigs infected with typhus The organs are triturated and suspended in physiologic salt solution for one half hour at 60° C Modifications of da Rocha Lima, Doerr and Pick Doerr and *Schnabel, Russ and Kirchner, Landsteiner and Hausmann, using other organs* especially brain, phenolized or glycerolized Inconstant results, not satisfactory

6 Adaptation of Snyder and Liu (1941) of the Zinsser and Castañeda Vaccine Suspension of peritoneal scrapings from mice infected with the European strain and irradiated with x rays (intraperitoneal inoculation of the virus)

7 Adaptation of Durand and Sparrow (1940) Using *Modification of Durand* and Giroud (1940) of the Castaneda Vaccine Utilizes rickettsias obtained from the specific pneumonia produced in mice by inoculation with the virus from lice intestines

Modification of Giroud and Durand (1940) using rabbit lung

These methods require selective application which varies according to whether one is dealing with epidemic periods or not whether work is being carried out in urban or in rural zones and in general depends on the epidemiologic variations which each disease has Thus for example in those countries where classical typhus exists some of the population can be protected from infection by the collective application of antigens composed of dead or of living organisms During epidemics however vaccines made of killed organisms are contraindicated although live vaccines may be used Serum prophylaxis may also be resorted to The use of combined serum and vaccine as proposed by Zinsser and Macchiavello (1936) and Macchiavello (1938) has not yet been tried in human beings for fear of an inadequate balance between the virus and the neutralizing serum Experimentally the method has proved to be excellent For typhus contacts serum protection is effective (Macchiavello 1938) However during large epidemics and under conditions of crisis and collective disorganization it has been demonstrated as in Naples during World War II that the elective control method is the use of insecticides with a residual activity This has the following additional advantages simple in application low in cost almost unlimited production of insecticides and lethal effect of insecticides on a large variety of disease vectors On the other hand vaccination confers a protection to the individual which is constant which means that an immunized person may move about and live exposed in infected regions with a factor of safety which is conferred by no other method of prophylaxis Vaccination is an acceptable method of protection for hospital personnel the Armed Forces in prisons asylums etc insecticides with residual action are best used in cases of emergency of social disorganization public calamities etc when faced with the beginning of an epidemic

VACCINATION

Vaccination against the rickettsial diseases is still in its initial phase The progress achieved during the past few years has been almost wholly that of vaccination against exanthematic typhus both in methods of vaccine preparation and in its application

Vaccines developed against the rickettsioses can be classified according to their antigenic specificity and therefore according to which rickettsial disease each vaccine is used against they can be classified also according to the state of viability of the component rickettsias or according to the immunizing material and its method of preparation distinguishing in this respect vaccines originating in infectious material (antigens) coming from arthropods from the organs or tissues of mammals from tissues cultivated in vitro or from in vivo cultures (fertile eggs) or finally according to the use made of the vaccine material whether to prevent infection with homologous virus or with heterologous viruses

Most of the vaccines are variations of a few methods, the multiplicity of denominations is hardly justified and serves only to cause confusion The immunizing power in laboratory animals of infectious products which contain

with typhus, the virus diluted or attenuated by cold or heat or disinfectants, or coated with substances such as lanolin or olive oil to retard absorption) Opposition to the use of this type of vaccine is due not only to the difficulty of standardizing it and to the failures which have taken place in attenuating the virus in those vaccinated, but also to the fact that the virulence of the blood from inapparent cases of typhus has been proved (Ramsine, 1929, Yu, 1931 Kuteischikow, Dosser, and Bernhoff, 1933, Balteanu and Constantinesco, 1937)

C Murine Typhus

I Vaccines Made With Killed Virus —

(a) **Vaccines Made With Virus From Arthropods —**

1 **Vaccine of Dyer et al (1932).** A triturate of fleas infected with murine virus, suspended in phenolized physiologic saline

(b) **Vaccines Made With Virus From Animal Tissues —**

2 **Vaccine of Zinsser and Castañeda (1931)·** A suspension of triturate of tunica vaginalis from guinea pig or rat, inoculated with murine typhus, in 0 85 per cent physiologic saline, formolized to 0 2 per cent

Modification of Zinsser and Castañeda (1932)· Methods were introduced to lower the resistance of the guinea pigs and rats, and especially to produce leucopenia, such as the action of cold, benzol, lack of vitamin C, and x rays Macchiavello (1936, 1938) tried thorium X, quinine, antileucocytic serum, etc, without favorable results The irradiation method, modified by Macchiavello and Dresser (1935) produced abundant rickettsias in the peritoneal exudates of rats without requiring costly installations, ordinary hospital x ray apparatus being used

3 **Vaccine of Castañeda (1939)·** Rats, mice, or rabbits are used and are inoculated by the nasal route with murine virus, a hepatization of the lungs due to rickettsial pneumonia occurs Vaccine is made by triturating the lungs and purifying the product by differential centrifugation Ten rats produce 1 Gm of rickettsias and 1 liter of vaccine is prepared from 10 Gm of the centrifugalized product Three doses are injected at intervals of 1 week

(c) **Vaccine Prepared With Murine Rickettsias in Tissue Cultures**—The methods applicable to murine virus are the same as those cited for classical virus Since the production of this type of vaccine is less than that obtained with the x ray method of Zinsser and Castaneda there has been little interest in its further development

(d) **Vaccine Prepared With Virus Cultivated in Living Tissue —**

4 **Vaccine of Cox and Bell (1939)** Prepared in fertile eggs according to the Cox method as for vaccine against exanthematic typhus *R mooseri* develops abundantly

II Vaccines Made With Living Virus —

Vaccines prepared with living virus have been developed not as a method of protection against murine typhus which is a benign disease, but as a method of developing a high cross immunity against exanthematic typhus The method is based on the following (1) murine virus can be easily attenuated to produce an inapparent or light disease in man, (2) this mild illness leaves a homologous and cross immunity of long duration, (3) immunity appears rapidly, more or less in 10 days, and lasts about 5 years, (4) large groups of people can be vaccinated in a short time, the usual source of virus being easily obtainable and practically inexhaustible, (5) vaccination can control an epidemic in 2 or 3 weeks if applied to all or a majority of the affected population, (6) only 1 inoculation is needed. These vaccines were developed in the face of the difficulty of obtaining large quantities of homologous vaccine against exanthematic typhus At present this difficulty has almost completely disappeared with the methods of vaccine production of Cox and of Castañeda

(a) **Vaccines Prepared With Virus From Arthropods —**

5 **Blanc Vaccine Adaptation of Blanc (1937)** Flea feces are dried under vacuum the fleas having been fed on typhus rats The feces are then emulsified and treated with

Modification of Combiesco, Zotta Manciulesco, Pop, and Tascau (1941) using dog lung

The preparation of these vaccines is dangerous, and personnel have been infected in practically all the laboratories where they are made (Zurich, 6 cases reported by Loffler and Mooser, 1942, Bucharest, 10 cases reported by Biraud, 1943) Previous vaccination does not prevent infection The vaccine has been used extensively in Madrid, Poland, Germany, and Romania, with good results Experimental studies of Topping and Bengtson, 1942 (1945) on the Giroud vaccine prepared by Plotz, showed good protection although inferior to that conferred by the alum precipitated Cox vaccine

(c) **Vaccines Prepared With Tissue Cultures of Rickettsias in Vitro** —

8 **Vaccine of Zinsser and Macchiavello** Nigg and Landsteiner (1930, 1932) adapted the Maitland Rivers technic to the cultivation of rickettsias Kligler and Aschner (1934) showed that these cultures produced protection when used as vaccines in guinea pigs Zinsser and Macchiavello (1936), introducing modifications to allow for large scale production, demonstrated the possibility of obtaining a vaccine with high antigenic potency Macchiavello (1938) showed further proof of the experimental value of the vaccine, but its application to human beings was postponed due to the development of the following method

9 **Vaccine of Zinsser, Fitzpatrick, and Wei (1939)** The original vaccine of Zinsser, Wei, and Fitzpatrick (1937) utilized cultures in agar tissue and was a simple modification of the Maitland method with the innovation of replacing the tunica vaginalis of guinea pigs first with rat embryos and later with chick embryos The vaccine was prepared as in the preceding method of Zinsser and Macchiavello

Modification of Zinsser, Plotz, and Enders (1940) In the preceding method the origin of the organisms was the tunica vaginalis of guinea pigs infected with European (classical) virus The authors changed the seed, using the vitelline membrane of chick embryos (Cox method) inoculated with classical typhus

(d) **Vaccines Prepared With Tissue Cultures in Vivo** —

10 **Vaccine of Cox and Bell (1939)** Vitelline sacs of fertile eggs infected by the method of Cox (1938) are used Wash in physiologic salt solution, remove excess liquid, and weigh Grind in a mortar with alundum and suspend in 10 per cent or more of physiologic saline

Add 1 per cent of phenol and 0 5 per cent of formol

Shake with glass beads for an hour, store at 2° C for variable lengths of time, and refine by differential centrifugation

Originally 3 doses 1 week apart were used for human vaccination According to Topping Bengtson, and Henderson, 1943 (1945), the different strains of classical typhus have equal antigenicity and can be used indiscriminately in vaccine preparation Craigie (1942) made a fundamental advance by introducing the ether extraction technic Topping and Bengtson following the procedure of Finlayson (alum precipitation), improved the strength of the Cox and Bell vaccine When Topping and Shear found the soluble substance mentioned elsewhere and proved its antigenicity, they preserved it in the vaccine along with the rickettsias The toxins evolved in the egg cultivations are destroyed with formalin

It has been chiefly with this vaccine that the most decided progress in vaccination against the rickettsial diseases has been achieved, the work of the investigators of the National Institute of Health of the United States Public Health Service being outstanding Thanks to these studies, the antigenic value of the vaccine has been improved and the number of required doses decreased

II Vaccines Prepared With Living Virus of Classical Typhus —

The trial of vaccination with living virus in exanthematic typhus (homologous virus) has only historical interest (Nicolle, 1916, Sparrow, 1924, Nicolle, Sparrow, and Conseil, 1926, Balteanu and Constantinesco, 1937, Combiesco, 1937, using blood or organs of animals infected

D Rocky Mountain Spotted Fever

1 **Vaccine of Spencer and Parker (1930)** Tick larvae are fed on infected rabbits (larvae of *D andersoni*) When they reach the adult state they are triturated the vaccine is purified and sterilized as in similar methods in which arthropods are used Good results have recently been reported by Parker

2 **Vaccine of Bengtson** Prepared in tissue cultures in Maitland media using Baker s instead of Tyrode s solution Good results on experimental trials

3 **Cox Vaccine (1939)** Prepared from rickettsias cultivated by the Cox method Good experimental results

Of these vaccines only that of Spencer and Parker has been widely used in man a positive reduction in the number of cases has been obtained in areas of great infectivity

E Other Rickettsioses

With the exception of São Paulo typhus, in which a vaccine of the Spencer and Parker type but using *I cajennense* has been developed the use of vaccines against the other rickettsial diseases, such as boutonneuse fever, has not progressed beyond the experimental stage

GENERAL CONSIDERATIONS ON VACCINATION AGAINST THE RICKETTSIOSES

In order that a vaccine against any of the rickettsial diseases be considered efficient, it should comply with the following requisites (1) innocuous for man, (2) easy to produce, (3) potent, that is produce a satisfactory and persistent immunity in vaccinated individuals, (4) easy to apply Regarding the last point, the most useful vaccines from the sanitary standpoint are those which require a single dose only

Killed vaccines are innocuous, that is to say, they are free of the danger of producing vaccinal typhus or of transforming inoculated individuals into virus carriers They have the following inconveniences (1) More than 1 injection, usually 3 are required Possibly alum precipitated vaccines will enable us to use a single dose (2) Large quantities of rickettsias are needed in their preparation, which has been a difficulty now obviated by the methods of Cox and of Castañeda (3) They produce immunity of short duration less than a year The recent work of Topping et al shows that immunizing power of typhus vaccines can be increased with the use of soluble antigen They showed also in a large group of vaccinated persons, that immunity decreased in about 5 months and was nearly gone at 9 months but that if "booster" doses are given there is an enormous rise in immunity within 2 weeks and this is maintained for long periods and decreases slowly

Living vaccines or virus vaccines have the advantage of producing rapid immunity, either by premunition or by premunition followed by immunity immunity is higher, more lasting (at least 5 years), and more ample in the sense that the virus vaccines protect not only against infection by homologous virus but also by related viruses, as is the case with the murine virus vaccine which protects against exanthematic typhus The quick immunity developed has suggested to some authors that this is due to a state of "precedence" ("preseance") (Blanc, Noury, and Baltazard 1935), which is that condition in which the presence of a living microorganism prevents superinfection with new doses of the same microorganism Minimal doses of virus are needed

bile at the time of use The method allows for standardization—1 mg equals 100 doses when dissolved in bile treated buffer solution

6 **Weigl Vaccine Adaptation of Sparrow (1939)** Lice are infected with the "Tunis I" murine virus by the Weigl method The final rickettsial suspension is introduced into man by the conjunctival route, immunity being developed by an inapparent infection

(b) **Vaccines Prepared With Virus From Animal Tissue —**

7 **Vaccine of Blanc (1933)** The technic of preparation is described in detail by Blanc (1936) A triturate is made of tunica vaginalis spleen, and suprarenal from guinea pigs inoculated with the Casablanca "IMC III" strain of murine virus and is diluted with 2 liters of physiologic saline At the time of use, 5 per cent sterile ox bile is added and allowed to act for 15 minutes The injection of the virus vaccine is made in the deltoid in doses of 1 0 c c for adults, 0 5 c c for children from 8 to 15 years of age, and 0 25 c c for the 1 to 8 year age group

Many experiences showed the method to be effective At first 19 volunteers were satisfactorily immunized Vaccination was then made in the prison at Adir in 1934 (723 individuals), in Ali Moumin in 1936 (823 prisoners), in Petitjean, Morocco, in 1935 (8,234 persons), and in 12,000 members of the tribe of Abu el Ahmed and in Casablanca more than 1 300 000 persons had been vaccinated up to 1938, according to Gaud (1938, 1939) Among native Moroccans, not more than 1 5 per cent had a mild reaction, without stupor and with good general condition (Baltazard, 1938) Among Europeans, up to one third of those vaccinated reacted to certain lots of vaccine In Chile, of 520 vaccinated 227 had mild typhus or a febrile reaction, and 5 deaths occurred (Quiros, 1935) The virus was recovered in guinea pigs (Vaccaro et al 1935, and Palacios, Chavez, and Avendano, 1935) According to the investigation commission designated by the Medical Society of Chile, there were about 800 vaccinated of whom 23 per cent had grave murine typhus In the conference of experts called by the League of Nations, Zinsser (1937) raised the objection that the Blanc virus was not stable Ciuca and Ionesco Mihaesti (1941) maintained that murine virus should not be imported into places where it does not already exist Mooser (1941) maintained that the greatest danger was that the murine virus might become epidemic virus There must be kept in mind the tendency to accept man as a reservoir of classical typhus and possibly of any rickettsial virus, after infection, although this may be inapparent and the individual may even develop immunity The innocuousness of the virus and the impossibility of its being transmitted by lice were demonstrated by Baltazard (1938), who opposed the points of view just mentioned Neither in North nor in South America is there acceptance of typhus vaccine made from living virus of any sort

8 **Vaccine of Nicolle, Laigret and Durand (1936)** This consists of a triturate of brains of typhus infected guinea pigs and rats, mixed with egg yolk, desiccated, and emulsified in olive oil The virus is not attenuated, but absorption is slow In Tunis, 32,481 vaccinations were made with it from 1935 to 1937, and subsequently around 100 000 In the first group there were only 13 cases of murine typhus caused by the vaccine, 8 of these in Europeans The use of this vaccine has stopped various epidemic outbreaks

Modification of Laigret and Durand (1937) Guinea pig and rat brains are mixed with sodium phosphate and then desiccated

Modification of Laigret and Durand (1939) Mouse brain is used instead of guinea pig and rat The vaccine is standardized at 200 mouse units per dose, the final vehicle is physiologic salt solution rather than olive oil A single dose is used. From May, 1939, to May 1940, 200 488 immunizations were performed with this vaccine, without a single case of "vaccination typhus

Scarification Vaccination of Laigret, Fabiani, and Vargues (1942) This is not an other vaccine but a new technic in applying the previous vaccine by cutaneous scarification The value of the method has not yet been proved

form water, 5 1,000, xylol in petroleum jelly, 90 drops to 30 Gm , 5 per cent solution of anisol, 2 per cent phenol, mercurial salves, benzine vapors, and a few commercial preparations such as Cuprex, Lauto, Antiparasite W, etc) Also, it was not always easy to rid clothing of parasites Primitive but efficient and economical methods are boiling and ironing For large scale use with the intervention of a specialized organization, we have the use of steam (the Serbian barrel, autoclave), dry heat applied for 1 hour at least, at 90° C storage of clothing for prolonged intervals, the use of sulfur (totally ineffective usually), and cyanide gas applied in closed chambers through the action of sulfuric acid on sodium cyanide, to obtain a concentration of the gas of about 10 grams per cubic meter, or the use of hydrocyanic acid gas, or still better Zyklon B

Repellents*

Howard summarized the action of the repellents known up to 1916 The military campaigns in the Pacific, and the great incidence of scrub typhus among the soldiers, brought about the need for active repellents against mites The more important now in use are dimethylphthalate, benzyl benzoate phenylbenzoate, 2 phenyl cyclohexanol, and dibutylphthalate All these have little toxicity and are only weak irritants of the skin, they retain their effectiveness after clothes are washed two or more times

Repellents are little used against ticks, fleas, or lice DDT has no repellent action The mixture of Indalone, Rutgers 612, and dimethylphthalate known as '6 2 2 '' seems to have a certain repellent activity against various insects Recently another repellent and insecticide has been recommended—"NMRI 448," which is said to be several times more active than dimethyl phthalate

Repellents are used by the so called "barrier" method—applying them to the exposed parts and to all openings in clothing, also by manual application to clothing by mechanical pulverization, or by immersing clothing in an emulsion of the repellent in water Dimethylphthalate is used in this way by making an emulsion of 7 5 parts of the chemical in 35 gallons of water containing 6 pounds of soap

Insecticides

Except for pyrethrum and a few dangerous (for the use of the public) insecticides such as hydrocyanic acid, most of the insecticides in present use in the control of the vectors of the rickettsial diseases were produced as a result of the war effort, the most important contributions being made by Americans and English Details and summaries of the experimental work carried out in the laboratories at Orlando, Florida, are found in Report 100 of the Insect Control Committee (1945) besides in the original publication of Annand et al (1944) Summaries and indices of the literature on DDT have been compiled by Roark and McIndoo (1944, 1946) and Roark (1944, 1945) The two most important insecticides in use against rickettsioses are DDT and 666 The

*See also Chapter 66

to produce attenuated or inapparent infection and the vaccine can be produced economically and in enormous quantities (for example a single guinea pig can supply 2 liters of the bile treated vaccine of Blanc) The risks are the production of vaccine typhus the variable titer of the vaccine and therefor irregularities in its action racial selectivity which implies that Europeans may develop vaccine typhus while natives do not and the creation of reservoirs of virus with the possibility of introducing murine virus in localities where it does not already exist

Although apparently there are appreciable advantages in the use of living vaccine of murine origin we feel that with the modern method of preparation of killed vaccines and of quantity production and their applicability to endemo epidemic areas the arguments for the use of living vaccines are weakened and the danger of producing not only vaccine typhus but as occurred in Chile grave and even fatal cases of typhus stands out against their use

Another point of great interest regarding vaccines is the measurement of their immunizing power The earlier technics consisted of guinea pig inoculation and subsequent infection to demonstrate the protection conferred by the vaccine Donovick and Wyckoff (1945) summarized the possibility of making this method more exact comparing the duration of fever in vaccinated guinea pigs with controls in testing vaccinal immunity Complement fixation tests are also used in determining the immunizing titer of vaccines But recent studies show that this is not a true test of protection since antigens heated at 60° C for only 4 minutes may cause a marked fixation of complement but confer no immunity On the other hand the neutralization test in the white mouse using serum from the vaccinated person has proved to be an exact measurement of the degree of immunity present and therefore is the best test of immunizing potency so far developed

Allergic Reactions—Some writers among them Roth (1945) have recently described serious allergic reactions in individuals receiving the Cox vaccine against typhus reactions due possibly to some residual allergen in the egg material used in preparing the vaccine

INSECTICIDES AND RODENTICIDES

Until recently the majority of the methods developed to control the vectors of the rickettsial diseases were directed against lice especially the methods of collective control Measures against fleas mites and ticks were mostly confined to personal endeavor (cleanliness the use of insect proof clothing removal of insects etc) mass protection against the vectors being little developed such as the ridding of agricultural areas of insects the use of antagonistic insects against the vectors (as *Ixodophagus* suggested by Brumpt for the destruction of the ticks which transmit Rocky Mountain spotted fever) etc The destruction of animal reservoirs had not been considered in detail

The majority of insecticides used against lice deserve only to be mentioned (10 per cent oil of wintergreen 15 per cent oil of turpentine, chloro

A summary of this work was presented by Soper (1945) at the First Inter American Congress on Typhus Fever in Mexico City

Viel and Romero (1945) ended an epidemic of exanthematic typhus in Chile by the exclusive use of DDT and pointed out the simplification of the campaign as compared with the previous control methods used in that country The Pan American Sanitary Bureau is making a study of the comparative value of prophylaxis with vaccine and with DDT in the control of typhus in Colombia and Guatemala

The effect of DDT on fleas has been investigated by Lindquist (1944) Smith and Davies (1944) Macchiavello (1946) Ludwig and Nicholson (1945) etc Stage (1946) sums up the forms of application In aerosol there is a transitory effect and the method is not recommended, DDT powder is used on floors rat burrows and burrows and nests of other reservoirs a 5 per cent solution in kerosene or any other oily solution is useful against larvae One gallon per thousand square feet of the 5 per cent suspension or emulsion should be used, 1 pound of 10 per cent powder suffices for a similar area Macchiavello (1946) studied the action of DDT on 14 species of fleas finding it equally effective in all working with fleas on their animal hosts he found DDT less effective against *Echidnophaga gallinacea* (Davis) and *H suarezi* In mass treatment a 2 per cent DDT powder is equally effective against fleas as the 5 or 10 per cent powders

The action of DDT against ticks must be considered in a different light from its effect on the other insects mentioned since generally one attempts to control ticks not in close relation to man but to the hosts of the ticks and with the areas where they abound whether dwellings agricultural areas or wild vegetation Observations of Smith and Gouck and of Gouck and Smith in relation to *A americanum*, demonstrated the efficacy of DDT against ticks also 5 per cent DDT powder in the amount of 3 pounds per acre killed ticks in all stages when applied to forage fields Rude and Smith (1944) and Rude (1945) found a similar effect of DDT on *A maculatum* on cattle the action lasting for 3 weeks The preparation "1037" (5 parts DDT, 47 parts resin 33 parts Hercolyn and 15 parts dibutylphthalate) had a residual insecticidal action of 3 to 6 weeks in Texas Blakeslee using 15 Gm of 10 per cent DDT powder on dogs and 1 pound per house controlled an intense infestation with *Rhipicephalus sanguineus* Gouck and Smith (1944) had equal results with dogs Powders have not been very effective against *D variabilis* but 3 pounds of DDT per acre has shown high tick mortality in agricultural zones

With regard to *Ixodes ricinus scapularis Dermacentor albopictus Amblyomma cajennense* (Wasicky and Unti, 1944) results are similar at times ineffective action of DDT in powder form slow but sure action when the substance is incorporated with an adherent which does not dry out This agrees with the experience of McDuffie with *A americanum* in Camp Bullis who at times was unsuccessful with as many as 40 pounds of 10 per cent DDT powder per acre

Results are not favorable with the argasids *Ornithodorus megnini O moubata* and *O turicata* Dove (1945) sums up the experiments carried out with DDT on insects dangerous to man

use of insecticides varies according to whether one is trying to control arthropods on living persons or beings, or in habitations, or in infested land areas and depends also on the biology and habits of the vector

(a) **"DDT" (Dichloro Diphenyl Trichloro Ethane).**—The action of DDT on human lice (head and body lice) was tested by Bushland, MacAlister, Eddy, and Jones (1944), using a 3 per cent powder. They found that DDT is the most effective agent against lice, although it does not kill the eggs However, its residual action destroys the new generation Clothing to which DDT has been applied may be washed repeatedly without loss of action of the substance, especially if the clothing has been impregnated with high concentrations of DDT in a volatile solvent Applied as a powder, using any type of pulverizer in doses of 1 ounce per person, DDT prevents reinfestation for about 1 month The epidemic of typhus in Naples was controlled with DDT alone Experiments with military prisoners (Ahnfeldt, 1944) and studies in North Africa (Sergent and Beguet 1944) showed the same favorable results as those of Payne Ortiz Mariotte, and Malo Juvera (1945) in Mexico

Publication of the detailed reports of Soper et al (1945) and Soper et al (1947) allows one to appreciate the results obtained in North Africa and in Naples Ten per cent DDT in pyrophyllite was tried out in the Maison Carrée Prison near Algiers, in the city and suburban areas of l'Arba, and among prisoners in a concentration camp (at times comparing DDT with MYL), with the following results DDT and MYL are powerful insecticides which achieve practically the eradication of lice in closed communities when applied every 15 days, in communities where the inhabitants work and live with a highly pediculous population, those treated even only once showed a low infestation a month after the application of DDT powder These treatments can be given effectively without removing the clothing of the individuals, using mechanical applicators

The increasing spread of the epidemic in Naples caused a transfer of activities to Italy and the report of Soper et al covers the period 1943 1945 The outbreak began in Italy in February, 1942, apparently brought in by a train coming from the Russian front filled with repatriated soldiers destined for hospitalization in Foggia and Bari Typhus began there in the hospitals, as it did in Naples in March The first case in the civilian population was reported in Aversa, about 12 miles from Naples, in April From July 1, 1943, to June 1, 1944, there were 2,020 cases in Naples (511 of which came from outside the city) with 429 deaths The height of the epidemic was reached in December, 1943 and it began to subside by January, 1944 The last cases occurred in April in Naples, and in May outside the city This result was obtained by the establishment, in December, 1943, of delousing services which achieved a total of 3 000 000 applications of DDT (and MYL) The operation was performed on clothed individuals by the use of hand operated dust guns Patients and their families, and the general population, were treated in fixed stations and in addition systematic dusting of certain areas block by block, of air raid shelters, etc , was performed

Morton (1945) cite a long list of substances effective against mites and mention 15 compounds capable of controlling 90 per cent of the mites in contaminated areas the best being ' 666'' in dosage of 10 pounds per acre at which dosage sulfur and DDT are both ineffective (Annand Lindusky and Morton 1945)

RODENTICIDES

Domestic and wild rodents are the principal reservoirs of the rickettsioses However the unrestricted use of rodenticides especially in rural or wild areas might interfere with the development of species of animals useful to man According to Ormsbee (1945) a good rodenticide should have the following properties high toxicity acceptability to rodents rapid action freedom from odor and taste stability, nontoxic for human skin no tolerance production easy solubility low cost easy manufacture abundance of the necessary raw materials etc

1 **Sodium Fluoroacetate (1080')**—Developed as a rodent poison in the United States this substance is very stable very soluble without odor or taste very active and rapidly absorbed by the intestines It is a white powder fine light nonvolatile and not absorbed by the skin It is dangerous because it is easily confused with flour or baking powder No known antidote exists It is used dissolved in water in amounts of 5 to 10 Gm per liter or on solid baits or mixed with cereals in similar dosage Toxicity for various animals is between 0 1 to 0 2 mg per kilogram (dog) to from 8 to 10 mg per kilogram (domestic mouse) It has been used successfully against domestic rats by Johnson Greeley Buhler Pryor Clark Gorman Kelly Treichler Trapido Wiley Landon Macchiavello (1945) and against rats and numerous wild animals by Cox Brown and especially Kalmbach Slover (1946) summarized the bibliography and Ormsbee wrote several general summaries Its comparative toxic value against *R norvegicus* (Dieke expressed in MLD mg /kg) is ' 1080 0 22/0 01 strychnine sulfate 4 8/0 4 ANTU 6 9/0 5 thallium sulfate 15 8/0 9 zinc phosphate 40 5/2 9 arsenic trioxide 138/13 red squill (reinforced) against females 133/10 against males 276/29 barium carbonate 148/340

The disadvantages of '1080 are its extreme toxicity the lack of an antidote and the fact that it can be washed away by rains The percentage of rodents killed with the poison varies with conditions Used under optimum control conditions the writer has obtained as high as 75 per cent destruction of the murine population in urban zones

2 **Alpha Naphthyl Thiourea** (ANTU)—The studies of Richter Dieke and of Richter and associates have shown that α naphthyl thiourea is a poison *the effect of which is practically limited to R norvegicus* and is therefore specific Studies and field work with ANTU have been made by Kifer (1944) Upton Wiley Leslie et al Macchiavello Woke Nicholson Ludwig and Grimsley etc (1945 1946) According to Richter ANTU works by causing overwhelming exudation into the pleural cavity of rats The author found it

DDT does not seem very useful against mites *Liponyssus bacoti* and *Echidnolaelaps echidinus* do not appear sensitive to it The author found no appreciable reduction in 6 different species of mites found on rats and mice both wild and domestic using 10 per cent DDT powder in areas where the reduction in number of fleas found free or on rodents was greater than 90 per cent A gamasid found on fleas which were killed with DDT in rat burrows treated with the insecticide appeared to be completely insensible to it

(b) The Gamma Isomer of Hexachlorocyclohexane (Gammefane 666)—Hexachlorocyclohexanone ($C_6H_6Cl_6$) is an amorphous solid optically active of which 4 isomers are known the alpha and beta being inactive as insecticides The gamma form makes up from 10 to 12 per cent of crude 666 and is difficult to obtain in the pure state It is very stable slightly soluble in water (10 p p m) Its penetrating and rather irritating odor is a serious disadvantage It dissolves well in xylol carbon tetrachloride methanol and benzine Perchlorethylene is used for spray vehicle as it is nontoxic and noninflammable Water emulsions are made using turkey red oil triton X 100 or Goulac as emulsifiers Its poisonous action is by contact or ingestion and as a fumigant It is not toxic for man but produces headache and mucosal irritation The following information is taken from Slade (1945) and Jenkins (1945)

666 was developed in England and has not been as extensively studied as DDT Its insecticidal activity has been proved against a large number of insects including fleas lice and mites It can be applied as a powder in solutions as emulsions or as a gas The last is obtained by volatilization on hot metal plates Mixtures containing 20 per cent of the powder can be diluted to 5 or 2 per cent

It is not yet clear how many times more toxic it is for insects than DDT but it is highly effective against many which are not affected by DDT We were interested in showing that various mites tested on cloth impregnated with a concentration of 666 of 4 Gm per square foot were inactivated in 32 seconds and extinct in 15 minutes In fields treated with 10 pounds per acre of 666 there was almost complete eradication of mites It is believed to be 10 to 20 times more toxic for lice and fleas than DDT and to have a longer residual action even in the open

(c) Other Insecticides —

Although DDT in 2 per cent emulsions has shown insecticidal action against head lice for 1 week (Busvine and Loeson 1945) as have powder forms other louse poisons have been strongly recommended among them the powder MYL (0 2 per cent pyrethrins 2 per cent n isobutyl undecylenamide 2 2 dinitroanisol 2 per cent and phenol S pyrophyllite to 100) and the emulsion NBIN (benzyl benzoate 68 pints DDT 6 pints methyl para amino benzoate 12 pints and Tween 80 14 pints this concentrate is diluted in 5 volumes of water before application)

Methyl bromide is used to destroy lice and nits in clothing The German preparation Lausete is 4 times less effective than DDT Annand Snyder and

side") and leaves by the other extremity ("clean side") For the en masse delousing of clothing bed clothing etc, cyanide chambers are used Clothing is mechanically ventilated before being returned

2 Control of epidemics

(*a*) Every report is immediately investigated The sick are hospitalized and the contacts are put under vigilance, the formation of new foci by contacts other than members of the family being investigated At times special brigades are required to discover occult cases which may work by house to house inspection



Fig 290—Portable hot water bath installation with attached chamber for delousing clothing by dry heat.

(*b*) Statistical control of mortality rates in the offices of registrars or of similar officials of hospitals cemeteries etc Also data on the number of sick in hospitals jails barracks asylums and other places of collective living including as far as possible factories and schools

3 Control of the means of dissemination of typhus This includes inspection of boardinghouses hotels theaters and other places of public gatherings, repression of vagrancy, disinfestation of public vehicles trains and other means of transportation repression of commerce in used clothing disinfestation of dwellings etc

4 Sanitary education An antityphus campaign requires an autonomous technical organization backed by sufficient legal powers

experimentally satisfactory but of less value than "1080" in field work Defects in the poison include the finding that rats become accustomed to it, that it is less effective against young rats and that its odor and taste are more marked than in "1080," in which these are almost nil An advantage is that it works as a contact poison as well as by ingestion Recently ANTU in 20 per cent powder has been mixed with DDT in 10 per cent powder, the mixture being insufflated in rat burrows and distributed along rat runs and galleries, killing both rats and fleas ANTU is almost insoluble in water but can be mixed with a large variety of baits It is not toxic nor irritating to man, and scarcely so for domestic animals

ADMINISTRATIVE METHODS IN PROPHYLAXIS

Prophylactic methods vary, principally in relation to the biology of the vector or reservoirs, to the special epidemiologic condition of each rickettsial disease, to ecology, and to the economic and cultural situation of the human group in which the disease occurs The administrative and legal measures of most value are those which have been developed in the control of exanthematic typhus

A Typhus Transmitted by Lice

In all countries where typhus is a disease of national importance, official control services have been developed backed by adequate legislation Typhus control measures may be divided into individual and collective

(a) Individual Methods of Typhus Control —

1 Declaration of cases

2 Investigation of the source of infection This is of fundamental importance In Valparaiso, Macchiavello and Grossi (1937) succeeded in tracing the lines of contagion in 90 per cent of cases

3 Isolation The sick should be hospitalized, the patient and his clothing receiving a careful delousing on admission

4 Quarantine Typhus contacts must be deloused, have their temperatures taken daily, and protected with hyperimmune serum in doses of 5 to 20 c c, depending on the potency of the serum They should be checked up to the maximum period of incubation of typhus In justified cases, quarantine camps have been constructed for typhus contacts

(b) Methods of Collective Prophylaxis —

Collective methods may be thus divided

1 Control of lousiness In rural zones, delousing by means of mobile brigades equipped with portable material for cutting hair and cleansing the sick and for disinsectizing clothing by dry or moist heat, in urban areas, the setting up of stations for bathing and disinfestation (called, in Chile, cleansing houses—*Casas de Limpieza*) These usually have sections for men and women and a general section for treating clothing They are designed so that a parasitized individual enters at one extremity of the building ("dirty

places where the typhus reservoir is *R norvegicus* a mixture of ANTU (20 per cent) and DDT (10 per cent) in pyrophyllite can be used to advantage The work of eradicating fleas from rat nests and burrows must be minute and complete A partial treatment of burrows does not result in a permanent reduction of the flea indices in the rats which comes to light especially after the use of poison when there then appear a few examples of rats with unusually high numbers of fleas per rodent (100 or more)

C The Spotted Fevers

Prophylaxis of the spotted fevers varies according to whether one is dealing with the North American types with São Paulo fever boutonneuse fever etc This is due chiefly to the vectors and to geographical localization When the ticks are prevalent in wooded areas and the cases occur in individuals who accidentally come in contact with these zones (woodcutters hunters tourists etc) prophylaxis is completely an individual matter (avoiding tick bites using adequate clothing with all openings provided with elastic wristlets anklets etc the prompt removal of all parasites found on clothing or body) In areas of greater incidence mass vaccination with the Spencer Parker or the Cox vaccine is recommend Anigstein Bader Young and Neubauer (1944) recommend the injection of immune serum around tick bites Armstrong and Topping decry this treatment (1944) Recently certain repellents have been shown to be somewhat effective against mites Also DDT may be useful in treating domestic animals which are tick hosts The use of ' 666 promises to be of value in treating terrain and dwellings in which infestation by these arthropods justifies measures of this nature

D Scrub Typhus

The previous considerations may be applied to the prophylaxis of any of the variants of scrub typhus As a result of war the United States Army developed a series of repellents and mite poisons which have been mentioned previously Also 666 promises to be a splendid residual eradicator against mites

E Q Fever and Trench Fever

The prophylaxis of Q fever by means of vaccination and sero vaccination in those exposed has been tried in Australia It is reasonable to assume that the extermination of the vector ticks and of the reservoirs by means of residual acting insecticides and of poisons such as 1080 will be tried in the future As regards trench fever under epidemic conditions the same delousing methods used in typhus should be applied

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(c) **Modern Methods of Typhus Control —**

Collective sero prophylaxis has eradicated epidemics of typhus in Mexico and in Chile Vaccination with living vaccines prepared from murine strains (Blanc in North Africa) is also a method that can be recommended Vaccination with killed vaccines prepared with homologous virus Cox or Castañeda types can be recommended as a permanent measure to be used in protecting populations subject to sharp typhus epidemics

The procedure of choice in cases of emergency is the use of 10 per cent DDT powder in doses of 1 ounce per person The powder can be applied with any sort of hand pulverizer or blower without undressing the individual blowing the powder into the openings in the clothing so that it reaches the innermost parts Davis Milo Juvera and Hernandez Lara (1944) studied the application of other antilouse powders and liquids in civil populations

B Typhus Transmitted by Fleas

It will be understood that in those rickettsial diseases which are chiefly rodent diseases transmission to man is possible only when a vector capable of transmitting the infection exists Generally the human incidence of this type called zootic by Megaw is low and accidental and therefore prophylaxis cannot be systematized nor follow common norms

Against murine typhus in urban zones general methods similar to those used against bubonic plague can be employed Macchiavello (1932) observed that the murine typhus in Antofagasta Chile increased after an intense campaign of deratization coincidentally with a transitory elevation in the *cheopis index* per rat Later the disease and the *cheopis* index dropped in parallel When the Antiplague Service in that city was terminated in 1939 murine typhus began to increase along with an increase in the murine population In the United States because of the notable increase in murine typhus the methods used in controlling bubonic plague were extended to typhus control To this end there was organized the Typhus Fever Control Unit of the United States Public Health Service which aided this work in various ways Eskey (1943) laid the foundations for murine typhus control recommending external rat proofing of edifices and rat and flea control within buildings by means of trapping poisoning and fumigation Some of the southern states have organized extensive studies and campaigns to this end The introduction of DDT as an insecticide and of 1080 and ANTU as rodenticides has simplified this work Henderson (1945) in Georgia outlined a procedure for controlling rat ectoparasites by the use of insecticides with a residual action recommending the use of 5 pounds of DDT per industrial establishment, 1 pound per residence in urban areas and 2½ pounds per barnyard in rural areas Treatment should be repeated each 3 months In Lavaca County Davis Rude and Brundrett used 10 per cent DDT followed by 1080 In this way the danger that fleas infected with typhus may attack man, when their hosts die is avoided The control of rodents and their ectoparasites with DDT and 1080 was carried out by Macchiavello (1946) in two Peruvian towns with excellent results In

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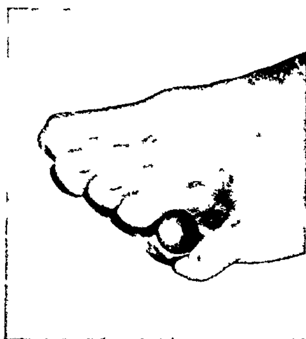


Fig ??1 —Initial lesion of rickettsialpox in interdigital space between the fourth and fifth toes. (A button has been placed between the toes to bring out the lesion more clearly)



Fig ?? —Primary lesion on left arm in crusted stage

PATHOLOGY

Biopsies of skin lesions and of a regional lymph node (Dolgopol 1948) showed essentially the pathology of rickettsial disease In the section of skin

CHAPTER 36

RICKETTSIALPOX

MORRIS GREENBERG

DEFINITION

Rickettsialpox is a disease of rickettsial origin first recognized in New York City in 1946 (Greenberg et al 1947a) It is characterized clinically by the appearance of an initial lesion followed in about one half to one week by an acute onset of illness with fever headache backache and other symptoms and then by a generalized papulovesicular rash The entire course from initial lesion to recovery is about 3 weeks

CLINICAL FINDINGS

The **incubation period** is 1 to 2 weeks

The **initial lesion** is a rounded firm red papule which grows until it attains a diameter of 1 to 1 5 cm The center becomes vesiculated and the vesicle then dries and shrinks forming a black eschar The skin around the papule is normal at first but later becomes erythematous There are no subjective symptoms After about 3 weeks the scab falls off leaving a small scar The regional nodes usually become enlarged but are only slightly tender The primary lesion may appear anywhere on the body and probably represents the site of entry of infection

The onset of symptoms is sudden with fever chills or chilly sensations sweats headache backache lassitude and photophobia The fever frequently reaches 103° to 104° F with morning remissions and lasts with the other symptoms for a week

The **rash** appears a few days after onset of symptoms The lesions resemble the initial lesion but are smaller At first they are maculopapular but become vesicular The vesicles then dry and the scabs fall off without leaving a scar They are generalized and discrete and may appear on mucous membranes They are rarely seen on the palms and soles They may be abundant moderate or scanty in number and last about a week There are no subjective symptoms

There are no other unusual physical signs or symptoms Pulse follows the fever respirations are normal heart and lungs are normal on physical examination and x ray There have been no complications and no deaths

LABORATORY FINDINGS

Except for a leucopenia the usual laboratory findings are negative The agglutination reactions for typhoid paratyphoid A and B tularemia brucellosis and leptospirosis are likewise negative The Weil Felix reaction with *Proteus* OX19 OX2 and OXK is negative during convalescence as well as dur

there were groups of mononuclear cells around the blood vessels The capillaries showed endothelial swelling which bulged into the lumen In some of the capillaries strands of fibrin were observed Mast cells were seen in the perivascular cellular aggregations around hair shafts and sweat glands and in the dermis Rickettsia like bodies were not observed

DIFFERENTIAL DIAGNOSIS

Rickettsialpox should be differentiated from the other rickettsial diseases and from some other diseases that it resembles clinically as follows

Chicken Pox —This is the disease with which it has most frequently been confused because the rash in both is vesicular In chicken pox however there is no initial lesion the papule becomes vesiculated in its entirety so that at certain stages only vesicles are seen and fever does not usually precede the rash The complement fixation test is specific for rickettsialpox

Smallpox —This disease is much more severe than rickettsialpox Headache and backache precede the fever The rash is vesicular at first but becomes pustular and lasts a long time Symptoms are severe and the mortality rate is high

Infectious Mononucleosis —A rash occurs rarely in infectious mononucleosis The blood picture is typical and the heterophile antibody reaction is positive

Other Rickettsial Diseases —The other rickettsial diseases are characterized by rashes which are macular maculopapular or petechial Only in rickettsialpox are the lesions typically vesicular Rocky Mountain spotted fever epidemic typhus and tsutsugamushi or scrub typhus are more serious diseases with fairly high mortality rate The Weil Felix reaction is positive with *Proteus* OX19 in Rocky Mountain spotted fever epidemic and endemic typhus and boutonneuse fever and with *Proteus* OXK in scrub typhus Only in rickettsialpox is the Weil Felix test negative Finally the complement fixation tests are specific except that some crossing occurs with Rocky Mountain spotted fever

ETIOLOGY

A rickettsial organism *(Rickettsia akari)* can be recovered from the blood of patients in the acute stage of the disease (Huebner et al 1946a) Mice which have received injections with such blood show inactivity rapid breathing and ruffled fur approximately 9 days later Pathologically they show a large edematous liver and a very large engorged spleen Suspensions of liver and spleen produce similar symptoms in other mice when passed serially In guinea pigs the suspensions cause scrotal swelling and fever in 3 to 4 days Suspensions of brain from the mice cause symptoms in other mice Brain suspensions will kill developing chick embryos in about a week when injected into yolk sacs and films made from the yolk sacs show numerous intracellular and extracellular tiny diplobacilli which stain well by the Macchiavello method Yolk sac suspension is easily transferred to other eggs and causes illness in mice and in guinea pigs similar to that caused by animal passage ma

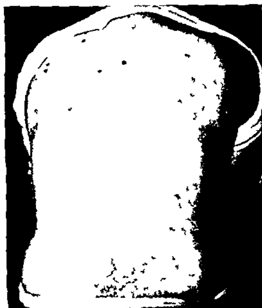


Fig 223.—Rash of rickettsialpox The rash is more marked over the lower back and sides



Fig 224.—Biopsy of primary lesion Mononuclear cellular infiltrates around a hair root and sebaceous glands Dark clumps beneath a sebaceous gland are mast cells. (Courtesy of Vera B Dolgopol)

obtained from the same shops by the sick and the well Milk was pasteurized the water supply came from the city system and was adequately chlorinated and the plumbing was in good sanitary condition

The environmental sanitation was good both in the houses and in the neighborhood ticks and mosquitoes were absent except for some specimens of *Culex pipiens* larvae found in a mosquito breeding impoundment in the basement of an unfinished house near by and specimens of adults of the same species found in some of the basements

The epidemiologic investigation incriminated the dwellings themselves as the site of the source of infection Numerous house or field mice *Mus musculus* were observed in apartments basements halls and courtyards and were heard in the walls of the buildings They were trapped and combed for ectoparasites These were recovered and identified as *Allodermanyssus sanguineus* (Hirst) Similar mites were recovered in mouse harborages and on incinerator walls in the basements They were blood sucking arthropods Smears made from those engorged showed mammalian erythrocytes

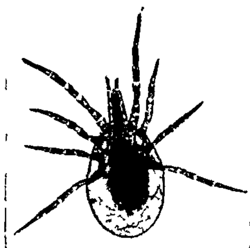


Fig ??6—*Allodermanyssus sanguineus* (Hirst) Adult stage

Mites from a number of pools were ground and injected intraperitoneally into male guinea pigs (Huebner et al 1946b) On the fourth day, fever and scrotal swelling were noted Tunica washings from these pigs were injected into guinea pigs and mice and caused characteristic illness They likewise killed chick embryos 7 days after inoculation into yolk sac and smears from the yolk sac stained by the Macchiavello method showed typical rickettsia like organisms Used as antigens in the complement fixation test they gave results similar to the organisms recovered from the patients blood

The final link in the chain was forged when *R akari* was also recovered from mice trapped in the buildings (Huebner et al 1947) The recovered organisms were identical with those obtained from the blood of patients and from trapped mites It appeared that infected mites survived and propagated

al It does not grow on acellular media The recovered organisms show igh degree of specificity when tested by the complement fixation reaction ainst sera from normal individuals, recovered patients, and cases of other seases including other rickettsial infections, except for cross reactions with ocky Mountain spotted fever Significant rises in titer can be demonstrated patients when blood is obtained early and later in the disease The sera f recovered patients will also give positive results when tested against Rocky Mountain spotted fever antigen in about 80 per cent of the cases, usually in lower titers, but will give negative results if tested against other antigens, in cluding those of the other rickettsial diseases The sera of recovered pa tients give negative Weil Felix tests with antigens of *Proteus* OX19, OX2, and OXK, except occasionally when they are positive in low titers

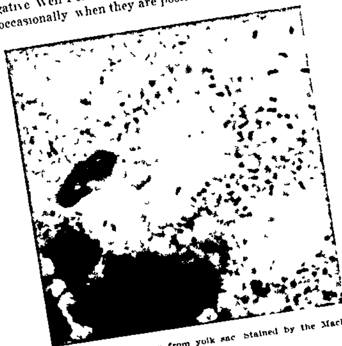


Fig 225 —Smear of *Rickettsia akari* from yolk sac Stained by the Machiavello method

EPIDEMIOLOGY

The original study was made in 1946 in New York City (Greenberg et al 1947b) An epidemic of an exanthematous disease occurred in one of th boroughs of the city and was sharply confined to a group of 69 three storie buildings in 3 blocks, each block consisting of 23 connected houses Appro imately 480 families, comprising 2 000 individuals occupied these dwelling Over a 3 month period 124 cases were found an incidence rate of 6 2 p cent equally divided between the sexes and approximately the same in ch dren and adults The residents had lived in the houses for years, and very had been away from the city in the month preceding the outbreak Occu tions varied widely, meals were not eaten in common, and food supplies w

CHAPTER 37

HELMINTHIASIS

(A) General Considerations (B) Nematodiasis or Diseases Caused by Nematodes or Roundworms (Ascariasis, Enterobiasis or Pinworm Infection, Strongyloidiasis, Necatoriasis and Ancylostomiasis or Hookworm Disease, Trichuriasis or Whipworm Infection)

Pedro Kourí

GENERAL CONSIDERATIONS

Helminthology is the study of worm parasites, or helminths General helminthology has progressed considerably in recent years We shall here consider only those helminths parasitic to man

Although the classification of the helminths used in this section does not always exactly follow zoological classification, we have adopted it for its simplicity and practical value in clinical work * For classification of the Helminths see Gradwohl and Kouri (1948) and Kouri and Basnuevo (1949)

HISTORY OF HELMINTHOLOGY

In 1838, Ancylostoma was discovered by Dubini in the intestines of the cadaver in a young man in a hospital in Milan

In 1851, *Schistosoma haematobium* was discovered by Bilharz, in Egypt, in the blood of the portal vein of man and was considered the causal agent of Egyptian hematuria

In 1835, *Trichinella spiralis* was found in man by Owen in England, later, in 1846, it was found by Leidy in pigs

Between 1852 and 1863, following the experiments of von Siebold, Kuchenmeister, Leuckart, and Naunyn, the life cycle of *Echinococcus granulosus* was described

In 1861, Leuckart, in 1863, Mosler, and others explained the life cycle of *Taenia saginata* while that of *T solium* was described by van Beneden in 1853, Haubner and Kuchenmeister in 1855, and Leuckart in 1856

In 1869 Fedtschenko, in Turkestan, showed that the larvae of *Dracunculus medinensis* penetrate into the *Cyclops coronatus* where they undergo metamorphoses

In 1873, Weinland suspected *Lymnaea truncatula* as the intermediate host of *Fasciola hepatica*, but experimental proof was made independently by Leuckart in Germany and Thomas in England in 1883, who described the complete life cycle

In 1882, Leuckart recognized that *Strongyloides intestinalis* and *S stercoralis* were the parasitic and the free living forms of the same nematode

In 1838, Perroncito, and in 1886 1887 Leichtenstern, first suggested the life cycle of *Ancylostoma duodenale*, but Looss, in 1896 1897, demonstrated penetration of the skin by the infectious larval form, and its migrations into the lungs, trachea, and pharynx, before localization in the intestine, where it develops into the adult stage

*Editor's note The original nomenclature of Dr Kourí has been changed in some places to conform to the more generally accepted usage in the literature on tropical medicine.

by obtaining blood meals from mice which served as a reservoir The survival and multiplication of mice was simplified by the presence of incinerators in the buildings These were not fired frequently and food accumulated in them so that they became excellent harborages for the animals When the infected mites were accidentally introduced into the apartments or when tenants visited the basements the mites attached themselves to the human beings and infected them

Since the outbreak was first studied cases have been reported in 4 boroughs of the city (Greenberg 1948) During 1946 (June to December) 177 cases were reported including those in the epidemic area in 1947 157 cases in 1948 141 cases and in 1949 107 cases Most of the sporadic cases have come from the boroughs of Manhattan and Bronx Multiple cases in a house are common Apparently the disease has existed in the city for a long time without being recognized Conditions being ripe an epidemic occurred in a restricted area which focused itself on the attention of the health authorities No cases have as yet been reported outside of New York City

TREATMENT

Rickettsialpox is a self limited disease The acute symptoms last so short a time that specific therapy is not essential The symptoms yield readily to the ordinary antipyretics and sedatives Aureomycin acts specifically in this as in other rickettsial diseases and chloramphenicol and terramycin although *not sufficiently tried appear to act likewise (Rose et al 1950)*

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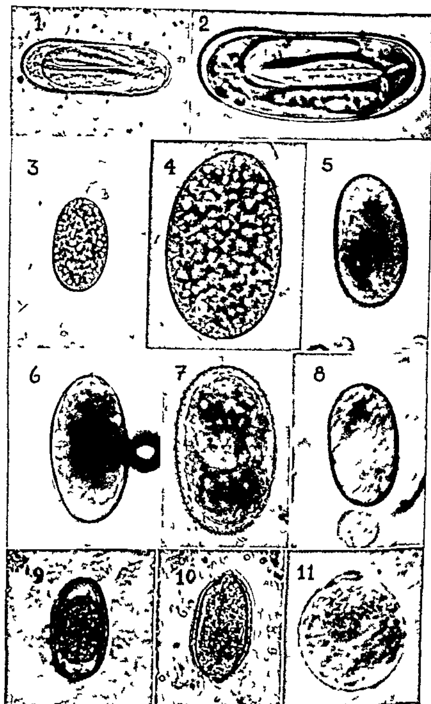


Fig 297—Microscopic pseudoparasites Eggs in transit and nonparasitic elements frequently found in human feces *1* and *2* Egg of *Heterodera radicicola* *3* to *8* eggs of *Tyroglyphus* sp in different stages of development *9* and *10* vegetable elements *11* pine pollen grains (Original photomicrographs)

In 1902, Stiles and Ashford simultaneously discovered a new hookworm, *Necator americanus*, as the cause of retarded mental and physical condition of the "poor whites" of the South in the United States (Stiles) and "tropical anemia" in Puerto Rico (Ashford)

In 1909 1913, Miyagawa, Fujinami, and Miyairi and Suzuki showed the intermediate host of *Schistosoma japonicum* to be a mollusk of the genus Oncomelania, and proved that the furcocercariae enter through the skin In 1915, Leiper described the complete life cycle of *S haematobium* and of *S mansoni*

In 1915, Robles, of Guatemala, noted for the first time the presence of onchocerciasis in America, and suspected the intermediate host to be a Simulium

In 1916, Stewart and, in 1920 1921, Ramson and Foster, demonstrated the migrations of the larvae of *Ascaris lumbricoides* in hepatic and pulmonary studies

In 1910 1917, Kobayashi, 1918 Muto, 1925 1926 Nagano, 1924 1927 Faust and Khaw described the life cycle of *Clonorchis sinensis* In 1915 1919, Nakagawa, 1906 Yoshida, 1917 Ando, in 1918 1921 Kobayashi and other Japanese authors described the life cycle of *Paragonimus westermani*, and in 1917, Yokogawa, Katsurada, and Muto, the life cycle of *Metagonimus yokogawai*

In 1917 1918, Janicki and Rosen described the complete life cycle of *Diphyllobothrium latum*, the last larval stages in the fish had been known since Braun first suggested it in 1883

In 1915, Leiper proved the intermediate host of *Loa loa* to be a Chrysops, and Kleine incriminated two African varieties *Chrysops dimidiata* and *C silacea* In 1926, Blacklock described the vector of *Onchocerca volvulus* in Africa as the *Simulium damnosum* In 1927 1928, Sharp was able to follow the complete life cycle of *Dipetalonema (Acanthocheilonema) perstans* in *Culicoides austeni* and *C grahami*, and in 1931 Strong showed that the intermediate hosts of *Onchocerca volvulus* in Mexico and Guatemala are *Fusimulium avidum*, *F mooseri*, and *F ochraceum*

In 1931 1933, Kouri and Arenas described the specific action of emetine hydrochloride in human fascioliasis hepatica Kouri, Basnuevo, and others described the clinical picture of this disease in man, and Kouri described an original technic for the diagnosis

In 1938, Luis A León described *Taillietina quitensis* in Ecuador

In 1938, Kouri, Macho Doval, Basnuevo, Cardelle, Rappaport, Sotolongo, and others reported a new parasite in human beings in Cuba, *Inermicapsifer cubensis* (Kouri, 1938) which Kouri had studied since 1935 in more than 45 cases of human parasitism

LABORATORY METHODS FOR THE DIAGNOSIS OF DISEASES CAUSED BY HELMINTHS

It is our belief that it is not always possible to make an accurate diagnosis of parasitism from the symptomatology alone, for often this is a presumptive diagnosis In countries where parasitism is frequent and is thoroughly investigated by laboratory methods one can usually make an accurate diagnosis with the aid of laboratory methods

Laboratory methods in helminthiases are discussed in Chapter 72 and will not be given here

NEMATODIASIS OR ROUNDWORM INFECTIONS

GENERAL CONSIDERATIONS

Nemathelminthes which include Nematoda, Gordiacea, and Acanthocephala, are invertebrate artiozoa with chitinous integument, usually conical or spherical spermatozoa with ameboid movements, unsegmented bodies, and without articulated legs The bodies are cylindrical and have celomic cavities filled with a liquid which bathes the genital and digestive organs The sexes are usually separate Most of the Nemathelminthes are endoparasites

1921, Ransom and Cram, in 1922, Koino and Koino, and in 1927, Ransom and Foster demonstrated that after the larvae have migrated through the body they develop into mature *worms in the intestine of man*

GEOGRAPHIC DISTRIBUTION

Ascaris lumbricoides is a cosmopolitan parasite, found in every part of the world, but is more abundant in tropical countries because the high temperatures aid in its development, and the poor hygienic conditions of certain tropical areas promote infestation

CAUSATIVE AGENT

Ascaris Lumbricoides Linnaeus, 1758
(The Large Intestinal Roundworm)

Synonyms—*Stomachida vermis* Pereboom 1780, *Stomachida pereboomii* Goeze 1782, *Ascaris suum* Goeze 1782, *Fusaria lumbricoides* (Linnaeus 1758) Zeder 1800, *Ascaris ovis* Rudolphi 1819, *Lumbricoides vulgaris* Méret 1821; *Ascaris suilla* Dujardin 1845; *Ascaris maritima* Leuckart 1876 (?), *Ascaris texana* Smith and Goeth 1904

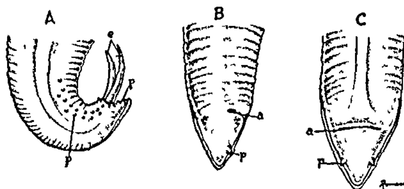


Fig 228—*Ascaris lumbricoides* *A*, Posterior extremity of the male lateral view *e*, spicules *p*, papillae *B*, Posterior extremity of the female, lateral view *C*, Posterior extremity of the female ventral views *a*, anus *p* papillae (Original drawing of Kouri and Basnuevo in Lecciones de Parasitologia y Medicina Tropical, courtesy of Editorial Profilaxis S A Havana.)

Ascaris lumbricoides is a large cylindrical worm tapering to pointed ends, with the anterior end thinner than the posterior Pink while alive, it turns whitish when fixed in formalin, and yellowish when fixed in alcohol

The females are usually 20 to 35 cm long, sometimes reaching 40 cm, and about 5 mm broad The males are smaller, 15 to 30 cm long and 2 to 4 mm broad

They are provided with a chitinous and resistant outer layer, transversely striated, and with two lateral narrow streaks extending along the entire body length; these longitudinal lines correspond to the lateral fields Female reproductive organs are often observed through the transparent parasite when viewed before a light

The mouth, at the anterior extremity, is provided with 3 lips, each convex on the outer surface and finely denticulated in the inner margin. One lip is dorsal, the other 2 latero ventral Between the lips is the infundibulum, at the bottom of which the mouth opens

At the part of the anterior third nearest the middle third of the *female* parasite is a narrower section, the waist A distinguishing characteristic of the *male* is the appearance of the posterior end, which curves ventrally.

Like all nematodes, Ascaris has a body wall limiting a celomic cavity, *within which cavity* are the reproductive and digestive organs, bathed in a liquid matter containing the ascaris toxin ascaron.

Nematodes are vermiform, elongated and cylindrical, whitish or pink, sometimes with dark bands. Some like *Ascaris lumbricoides* are large, others like *Trichinella spiralis* and *Strongyloides stercoralis* are very small. The relative lengths and widths vary, the filaria being long and slender and the Ascarides long and rather thick. At the anterior extremity they at times show lips, at times papillae, at times a buccal capsule. The posterior end is thin and usually straight in the female and cylindrical conical and dorsally or ventrally coiled in the male or it may show cuticular expansions (alar appendages or alae) or more developed expansions (*copulatory bursae*). Males are smaller than females.

Certain **microscopic pseudoparasites** may be confused with nematodes, all those microscopic elements found in secretions or excretions of man which might be confused with actual parasitic elements.

(1) **Elements in Transit.**—Eggs, larvae, etc., of Nemathelminthes of animals or vegetables swallowed by man in food may merely pass through the alimentary tract without causing parasitism and undergo but slight modification or no modification at all. Other nonparasitic elements are vegetable cells, pollen grains, etc., swallowed with food, which may be mistaken for eggs.

(2) **Elements Derived From Outside Contamination.**—This includes those elements in (1) above, but these are microscopic elements which contaminate the stools after passage.

Examples of microscopic pseudoparasites of parasitic nature in simple transit are eggs of *Heterodera marioni* swallowed with tubers when these are parasitized by *H. marioni*, the larvae of *Turbatrix aceti* swallowed in vinegar with olives and in certain fermented liquids, likewise the eggs, larvae and adult forms of various species of Tyroglyphus swallowed with food.

Microscopic pseudoparasites in transit include various vegetable cells or pollen grains often erroneously interpreted as parasitic elements. Examples are eggs of an Oxyuris of the cockroach, larvae of *Turbatrix aceti*, eggs and larvae of flies. Eggs, larvae and adult forms of Tyroglyphus can be carried by the wind and may drop on the feces or into the concentration solutions. Pollen grains may also be carried by the wind and fall into the feces in uncovered containers, to be found later in microscopic examination.

The diagnosis of the various nematodiases is discussed separately under each parasite and will not be given here.

DISEASES CAUSED BY WORMS BELONGING TO THE ORDER ASCARIDATA

Ascariasis

(Parasitism Produced by *Ascaris lumbricoides*)

Synonyms.—Ascarid (Ascaris) or large roundworm infestation.

HISTORY

This parasite is called *lumbricoides* because of its similarity to the earthworm. It was known to the Greeks and Romans by the name *lumbricus teres*.

In 1863 Davaine observed that the ingested eggs were hatched in the intestine of man. In 1916 Stewart discovered the migration of the larval form through the lungs of rats. In

as a result of the moderate pressure of the cover glass on the slide, as in fertilized eggs, but if the pressure increases they are totally destroyed and disappear from the preparation These eggs show large refractive granules, similar to drops of fat, occupying the whole egg cavity and lacking a limiting membrane proper

Life Cycle

The fertilized adult females lay eggs in the intestine of the host, and the eggs are passed with the stool Outside the body the time required for embryonation varies according to the temperature 9 to 13 days under optimum conditions (22° to 23° C) in dark moist places Once the egg has embryonated, it becomes very resistant, and can live for a long time in an external medium, resisting freezing putrefaction and temperatures as high as 42° C Moist temperatures of 70° C and higher kill the egg Direct heat from the sun is extremely harmful to them

The embryo undergoes an intraovular molting in an external environment and becomes infestive, enters the mouth of the host through various mechanisms (food material contaminated by flies, etc) is swallowed and enters the duodenum The intestinal juices soften the eggshell, stimulating the movements of the intra ovular embryo which emerges through an opening of the shell as a vigorous larva 0 2 to 0 3 mm by 13 to 15 microns

The larvae bore through the wall of the small intestine into the lymphatic and mesenteric vessels and enter the lungs through the right heart They remain in the lungs for several days undergo a second and a third molting on the fifth or sixth and the tenth days respectively, then penetrate into the capillary and alveolar endothelia to reach the pulmonary alveoli From here they enter the bronchioles, bronchi and trachea then migrate up to the epiglottis They are then swallowed, pass through the stomach and reach the duodenum Here they undergo a fourth and last molting between the twenty fifth and twenty ninth days They develop into adult males and females 60 to 75 days after ingestion of the egg

From the lungs, the larvae may accidentally return to the heart by way of the veins, particularly in massive infestations They pass through the left ventricle into the general circulation and localize in different organs and tissues of the host, such as the lymphatic glands thyroid thymus spleen brain, and spinal cord, where they may cause clinical manifestations They may accumulate in the kidney to be passed with the urine or they may enter the placenta and fetus

The usual habitat of this parasite is the small intestine of man In erratic parasitism it may be found in any other part of the digestive tract The number of parasites ranges from 100 to 200, in exceptional cases there may be more than 1,000 usually there are only 8 to 10

The life span is unknown

A lumbricoides which infests man is morphologically identical to *A suum* of swine, but biologically they are different species Koino and other investigators have demonstrated that the Ascaris which parasitizes man cannot be transmitted to swine and vice versa

PATHOGENESIS AND PATHOLOGY

Certain individuals can tolerate the parasitism very well even when they harbor a great number of parasites With only a few parasites others may show important clinical manifestations a fact commonly noted in most helminthiases

The *fertilized eggs* are ovoid 50 to 75 by 40 to 60 microns The shell is formed by 2 membranes, the outer, festooned or mammillated the inner smooth, stout, colorless, and refractive There is a spherical sharply limited granular protoplasm within the egg, but not occupying the whole of the egg cavity

The *unfertilized eggs* are very atypical the morphology extremely variable They are generally larger and longer than fertilized eggs even though some are small, then their size and appearance vary The shell is much thinner They lose the outer mammillated shell

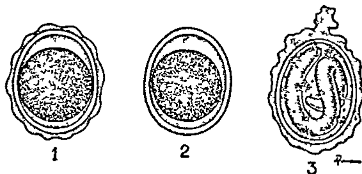


Fig 299—*Ascaris lumbricoides* Typical fertilized eggs *1* and *2* Containing a single cell *2* has lost the outer covering from the pressure of the cover glass *3* containing a vermiform embryo (Original drawing of Kouri and Basnuevo in Lecciones de Parasitología y Medicina Tropical courtesy of Editorial Profilaxis S A Havana)

Fig 300—*Ascaris lumbricoides* Unfertilized eggs *1* and *4* Removed from the uterus of the female parasite—these have scalloped external shell *2* and *3* *5* to *8* in feces—these have lost the scalloped external shell from the pressure of the cover glass (Original drawing of Kouri and Basnuevo in Lecciones de Parasitología y Medicina Tropical courtesy of Editorial Profilaxis S A. Havana.)

Mechanical Action

When A. *lumbricoides* occur in great numbers they may twist together and form large balls causing intestinal occlusion with serious consequences. They may also cause *hernial strangulation*.

Erratic Ascaris

Under certain circumstances Ascaris tends to leave the small intestine and travel through various parts of the body. This is called *erratic parasitism*. It may migrate to the stomach and be expelled by vomiting with alarming



Fig. 231.—*Ascaris lumbricoides*. (Autopsy of a case of Salas Jimenez and Cuernica in the Children's Municipal Hospital of Havana.) Gangrene and perforation due to ileo-ceco colic invagination with peritonitis resulting from ascariasis and trichuriasis. Anatomical specimen in the Carlos Finlay Museum of the Institute of Tropical Medicine, University of Havana. (Courtesy of Revista de Medicina Tropical y Parasitologia 2, No. 5, 1936.)

symptoms: fainting, cyanosis, cold sweats, filiform thready pulse, vertigo and nausea. More often it travels to the large intestine and is expelled through the anus. It may migrate to the esophagus, thence into the *larynx* and the trachea causing asphyxiation. From the pharynx it may penetrate into the Eustachian tube, perforate the eardrum and reach the external ear or ascend through the nasal fossae, enter the lacrimal ducts and emerge in the internal angle of the eye.

Pathogenesis refers to the mechanism by which the parasites act upon the organism which harbors them The following actions are the most common

Spoliative Action

Withdrawal of nutritive substances from the host is called *spoliative action* and is an important consideration in hyperparasitized children Ascaris takes from its host substances necessary for nourishment and development—chyme or blood It has been much debated whether or not Ascaris is hematophagous, that is whether or not it feeds on blood Investigations and experiences toward this end seem to demonstrate that Ascaris does not feed on blood or, if so only exceptionally

Toxic Action

The liquid from the celomic cavity of Ascaris is irritating to mucosae and may produce allergic phenomena as urticaria and asthma Chimamura* and Fugii isolated a toxin from Ascaris which they called *ascaron* Ascaron injected into horses may cause death Intradermal injection of Ascaris extracts can cause anaphylactic shock in patients who harbor the parasite Hypersensitivity of such individuals can be passively transferred to guinea pigs by injecting the guinea pigs with sera of such patients after this sensitizing injection The guinea pigs may die if they are reinjected with the celomic liquid of Ascaris

Certain clinical phenomena observed in ascariasis such as epileptiform and eclamptic attacks neuritis and paralysis have been attributed to the action of Ascaris toxin on the nerve cells Objections have been raised to conclusions that such symptoms are caused by the Ascaris for the reason that this parasite favors development of intestinal bacteria which can produce neurotoxins and these bacterial toxins and *not* the Ascaris toxin would then be responsible for such phenomena

Traumatic or Infectious Action

Ascaris can produce lesions of the intestinal mucosa by means of its powerful denticulated lips Occasionally Ascaris has been found in the peritoneal cavity According to Blanchard these worms may enter the peritoneum through abscesses of the intestinal wall caused by pyogenic bacteria inoculated into the lesion of the mucosa produced by the bite of the Ascaris At times one finds neither intestinal lesions nor scars thus Brumpt believes it possible for the young Ascaris to bore through the intestine and then develop as erratic parasites in the peritoneum

Ascaris may not only carry bacteria from the lumen of the intestines to the biliary and pancreatic ducts but may also inoculate the intestinal mucosa with bacteria It has been much debated whether or not Ascaris can inoculate the mucosae with typhoid bacilli or whether both the worm and the bacilli are ingested simultaneously in epidemics of typhoid fever where parasitism by Ascaris is also present and frequent

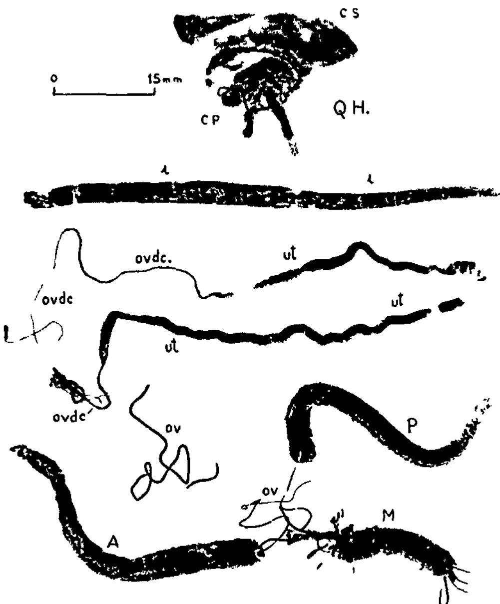


Fig 234 —*Ascaris lumbricoides* Ascaridian hepatic nodule removed by Noabo and Alvoré during operation for cholecystitis calculosa. *Q H* Hepatic tumor containing portions of a large female *A lumbricoides* within the cystic cavity The other objects in the photograph are remnants of the same Ascaris found in the cystic cavity which was left in the liver *i* intestine *ut*, uterus *ovdc*, oviducts *ov* portion of the ovaries *A M*, and *P* anterior central and posterior portions of the same female *A lu bricoides* (Original photograph)

In massive parasitism it may bore through the pancreatic ducts, the bile ducts, the gall bladder, and even the intrahepatic bile ducts, which it may obliterate

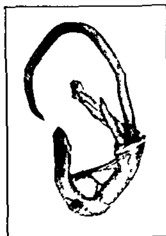


Fig 232—*Ascaris lumbricoides* in the lumen of an appendix Anatomical specimen in the Carlos Finlay Museum of the Institute of Tropical Medicine University of Havana.



Fig 233—*Ascaris lumbricoides* Photograph of the liver (autopsy by Castillo and Salas) showing the parasites in the common bile duct, gall bladder and intrahepatic ducts Anatomical specimen in the Carlos Finlay Museum of the Institute of Tropical Medicine University of Havana. (Courtesy of Archivos de Medicina Interna, Havana 3: No 3 1937)

Ascaris has been known to enter the appendix and cause intense pain, which disappears after the parasite has been expelled Occasionally an acute appendicitis develops especially if the parasite *remains in the same site, which* favors bacteriologic action At times it may even perforate the appendix

worm is filled with barium and can be seen as an opaque line. In addition radiography is advantageous in diagnosis because it may help to detect the location of the parasite.

PROGNOSIS

In general prognosis is favorable, particularly if the diagnosis is properly made. Even in severe cases, if the diagnosis is made in time and proper treatment is instituted, a rapid cure may be obtained.

TREATMENT

There are two very efficacious agents in the treatment of *A. lumbricoides*—chenopodium and hexylresorcinol. Santonin is no longer recommended since the curative dose cannot be tolerated.

Oil of chenopodium is administered as follows: Children are given 2 drops per each year of age, and adults are given up to 1.5 Gm. as total doses together with castor oil given in the morning on an empty stomach, and a saline purgative 4 hours later if there has been insufficient evacuation.

Oil of chenopodium gives the best results. Carbon tetrachloride or tetrachloroethylene with chenopodium reinforces its anthelminthic action. This last drug has given excellent results in the treatment of triple infestation by *A. lumbricoides*, *Necator americanus* and *Ancylostoma duodenale*.

Hexylresorcinol* (1,3-hydroxy-4-hexylbenzene) has also been used very successfully in doses of 1 Gm. for adults and 0.6 Gm. for children under 6 years of age, and 0.8 Gm. for children between the ages of 6 and 10, in capsules of 0.2 Gm. each, given in the morning after a night's fast. A saline purgative is administered 2 hours later. Combination of this drug with tetrachloroethylene has been recommended in Cuba by Basnuevo and Kouri. Hydroxylene in doses of 10 capsules for adults, each capsule containing 0.1 *Gm. of the 1,3-hydroxy-4-hexylbenzene and 0.30 c.c. of tetrachloroethylene.* Children are given 1 capsule for each 2 years of age. It is very efficacious, not very toxic and is easily administered. This is the best treatment in associated helminthiasis, particularly Ascaris with Necator, and is of great value in anthelminthic campaigns.

PREVENTION

Epidemiology

In Cuba this parasitism is much more frequent in rural districts than in cities. This can be explained on the basis of the different hygienic conditions under which people live in these regions. In rural districts infected persons disseminate the eggs of the parasite by defecating on the ground. Rains and floods carry the feces over broad areas and disseminate the eggs, thereby contaminating vegetables and drinking water. People who live in such regions are therefore constantly exposed to the danger of eating food contain-

*Editor's note (O. F.). In the United States Caprokol and Crystoids are used; these contain hexylresorcinol in 0.1 and 0.2 Gm. capsules. The same dosage as above is recommended.

Ascaris has also been found in pulmonary abscesses in caseous t glands in the pleural cavity peritoneum bladder vagina urethra formation of fistulas or abscesses

Irritative or Inflammatory Action

When found in great numbers Ascaris causes chronic irritation testines resulting in intestinal catarrh with consequent diarrhe dysenteric syndrome It is possible that this intestinal disturbance penetration of *Salmonella typhosa* and other pathogenic intestinal bac

SYMPTOMATOLOGY

Gastrointestinal Disorders.—Intense parasitism with Ascaris pr following symptoms pain in the stomach sensation of epigastric difficulty in digestion abdominal swelling and at times vomiting rhea Appetite may be exaggerated decreased at times absent At picture may simulate a real typhoid or dysentery or even a cholerif Ascaris can also provoke appendicular pain or it may produce purative appendicitis or symptoms of duodenal and gastric ulcer

Nervous Disorders.—These may be motor sensory and psychic convulsions *epileptiform* attacks paresthesia and paralysis etc vi neuritis delirium, hallucinations, etc Meningitic complications nightmare physical and mental arrest etc can also be observed vegetative disorders may at times be observed—tendency to vertige cope—disorders which are in reality caused by *toxic action on* t nervous system rather than by simple reflex phenomena since the syr not subside immediately after expulsion of the parasites but some

Allergic Phenomena.—Asthma urticaria pulmonary disorder philia Loeffler s syndrome may develop For other symptoms see t on pathogenesis and erratic Ascaris

DIAGNOSIS

Direct microscopic examination of feces and concentration met stitute the usual procedures in diagnosis of this parasitism Cons aminations at several days intervals should be practiced

In gastroduodenal and biliary localization of the parasite egg found by examining duodenal contents (Kouri and Basnuevo 1933)

If the host harbors only male Ascaris the microscopic diagnosi negative

If the patient harbors *young* females which are not yet able to the microscopic examination is also negative

If the host harbors one or more adult females but no males or yo incapable of fertilizing the females unfertilized eggs will be found in

In cases of ascariasis due to *male* Ascaris diagnosis can be mad ologic examination Sometimes the body of the Ascaris can be seen as space in the opaque barium shadow and at other times the intesti

CAUSATIVE AGENT

Enterobius Vermicularis (*Linnaeus 1758*) *Leach, 1853*

(The Human Pinworm or Seatworm)

Synonyms — *Ascaris vermicularis* Linnaeus 1758, *Oxyuris vermicularis* Bremser 1819 *Oxyurias vermicularis* Stiles 1905, *Fusarella vermicularis* Seurat 1916

E vermicularis is a whitish, very small worm It was described by Linnaeus in 175[illegible] The posterior extremity of the female is very long and sharp, of the male, conical an[illegible] coiled In the anterior extremities of both are 2 striated vesicular expansions of th[illegible]

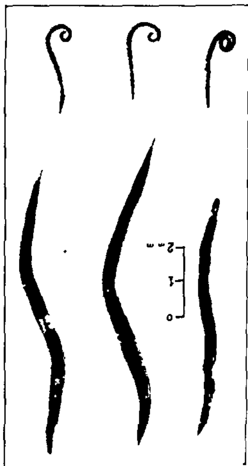


Fig 235 —*Enterobius vermicularis* *Above*, 3 females *below*, 3 males (Original figure [illegible] Kouri and Basnuevo)

cuticle The mouth has 3 retractable lips, without teeth, 1 dorsal, 2 lateroventral Tw[illegible] prismatic lateral ridges, which are very characteristic, extend longitudinally on each sid[illegible] of the body. The male is 2 to 5 mm long, the female 9 to 11 For further descripti[illegible] details, see Gradwohl and Kouri (1948).

The *eggs* are oblong, asymmetrical, flat on one side and convex on the other, about 6[illegible] by 30 microns. They have a double wall Because of the albuminous nature of the externa[illegible] wall, *the eggs adhere to each other, forming a cluster* The two walls of the eggs are com[illegible] pletely separated from each other except at a very small zone in the cephalic pole, on th[illegible] convex side The eggs are embryonated at the time of laying, containing the gyriniform[illegible]

ing embryonated eggs of the parasite and becoming infected. On the other hand, warm climates favor rapid intra-ovular development of the eggs, the infestive forms within 10 to 15 days, which explains the high percentage and intensity of parasitism among farmers in Cuba. In large cities like Havana with modern sanitation facilities and adequate sewage disposal the parasitism is less frequent and not so intense and parasitized patients do not spread the parasitic eggs.

Nevertheless, mild infestations (1 or 2 Ascaris) are possible and even relatively frequent in Havana if one eats fresh vegetables like lettuce and water cress which have been cultivated outside the city limits on lands contaminated by human excreta used to fertilize the soil. This type of soil fertilization, practiced by some Chinese farmers in Cuba, is contrary to sanitary ordinances.

Individuals who by their customs, appetite, occupation, age, etc., are more readily exposed to contamination, such as farmers, miners and children, are more frequently and intensely parasitized. Not only are children and young animals more frequently exposed to infestation, they are more susceptible than adults and older animals. Adults are in a state described by Brumpt as "natural periodic immunity."

Prophylaxis

General prophylaxis is the same as for other intestinal parasites:

1. Education.
2. Building of latrines, banning use of human excreta as fertilizer.
3. Finding the sources of infestation through coprologic surveys.
4. Treatment of parasitized patients.

Individual prophylaxis consists in preventing ingestion of embryonated eggs, the infestive form, along with contaminated food.

The following measures are recommended:

1. Filtration or boiling of water.
2. Thorough washing of vegetables with water that is not contaminated or that has been boiled, or abstinence from eating raw vegetables coming from parasitic sources.
3. Protecting food from flies and other mechanical vectors.

Enterobiasis

Pinworm Infection

(Parasitism Produced by *Enterobius Vermicularis*)

Synonyms.—Oxyuriasis, enterobiasis, pinworm infection.

HISTORY

This parasite has been known since ancient times. It was first described by Linnaeus in 1[illegible]8.

GEOGRAPHIC DISTRIBUTION

It is a cosmopolitan parasite.

CAUSATIVE AGENT

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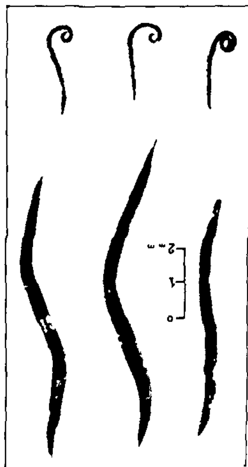


Fig 235 —*Enterobius vermicularis* *Above* 3 females *below*, 3 males (Original figure Kouri and Basnuevo)

cuticle The mouth has 3 retractable lips, without teeth, 1 dorsal, 2 lateroventral T prismatic lateral ridges, which are very characteristic, extend longitudinally on each s of the body The male is 2 to 5 mm long, the female 9 to 11 For further descript details see Gradwohl and Kouri (1948)

The *eggs* are oblong, asymmetrical, flat on one side and convex on the other, about by 30 microns. They have a double wall Because of the albuminous nature of the extern wall, the eggs adhere to each other, forming a cluster *The two walls of the eggs* are co pletely separated from each other except at a very small zone in the cephalic pole, on t convex side The eggs are embryonated at the time of laying, containing the gyriniform

or tadpole shaped embryos. In a few hours, under the favorable conditions of humidity and temperature of the rectal mucosa and the anus, the embryo passes into a second folded vermiform embryonal stage There it remains in the eggs and is found in the feces, together with numerous females, or it may be found in the groove between the buttocks

Life Cycle

The embryonated eggs laid by the females in the rectum and anus of the patient are immediately infective, which accounts for the autoinfestation in this helminthiasis

The embryonated eggs enter the host through the alimentary canal, reach the stomach and duodenum where the digestive secretions soften their walls, permitting the embryos to escape, the embryos then grow in situ Without further migration they undergo 2 moltings before reaching the adult stage with subsequent differentiation of the sexes

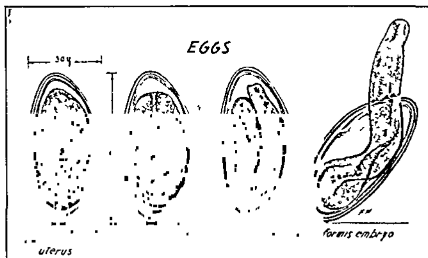


Fig 236 —*Enterobius vermicularis* Various final stages in the development of the eggs (Original)

After copulation the male and female pass into the large intestine where their life cycles continue The uteri of the gravid females are greatly distended by the large number of eggs A special type of tropism causes the female to migrate toward the anus where by biting it causes most intense itching, especially at night This itching causes the host to scratch himself, and the parasites are torn up and carried under the nails, or are expelled with the feces The males generally remain in the cecum and appendix where they ultimately die The duration of this cycle in the female is 2 to 3 weeks, which favors spontaneous recovery if there is no autoinfestation

The egg is an essential microscopic finding for a correct diagnosis of parasitism by *E vermicularis*, but its presence is not constant in the feces of parasitized individuals because the female parasite does not lay eggs in the intestine but migrates to the rectum and anus and there lays the eggs, or empties the uterus after leaving the body

EPIDEMIOLOGY AND SYMPTOMATOLOGY

The group of symptoms produced in infestations with *E. vermicularis* is called *enterobiasis* or *oxyuriasis* The infestation is more frequent in children and in women than in men When mild, it is easily tolerated, causing only

slight disturbances but when massive the clinical symptoms may be serious and affect the general status A mild infestation may become massive through autoreinfestation

Serious disturbances may occur in the digestive nervous and genital systems and may lead to a general systemic instability In the digestive system pruritus ani is the most constant symptom It is usually intense during the night it becomes almost unbearable Due to the violent scratching the perineal and perianal regions are traumatized, congestion and inflammation follo many hemorrhagic zones develop the cutaneous surface is covered with a bloody mucous excretion containing the gravid females and eggs of the parasite Similar lesions occur in the rectum Chronic catarrhal inflammation develops in the intestine This inflamed mucosa produces mucous secretions frequently blood stained and containing numerous eggs and parasites

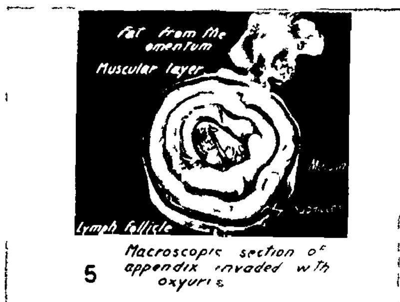


Fig 37 —Enterobius vermicularis Macroscopic section of appendix with the parasite (Original)

Enterobius frequently produces lesions in the appendix Bacteria present in the intestinal flora which usually do not cause disease penetrate through the lesions and become active thus causing enterobial appendicitis

Among nervous disturbances are changes in character the individual becomes sad irritable and sometimes melancholic If the infestation is not treated rather promptly this may lead to a definite neurosis or even a psychosis In children it may lead to epileptiform or hysteriform spells convulsions chills dizziness diminution of vision and hearing tinnitus aurium and incontinence of urine

Disturbances of the genital system are very frequent—erections erotic dreams seminal discharges onanism nymphomania and menstrual disorders The parasites may migrate from the anal region to the vulva and the vagina

or tadpole shaped embryos In a few hours, under the favorable conditions of humid and temperature of the rectal mucosa and the anus, the embryo passes into a second fold vermiform embryonal stage There it remains in the eggs and is found in the feces, gether with numerous females, or it may be found in the groove between the buttocks

Life Cycle

The embryonated eggs laid by the females in the rectum and anus of the patient immediately infective, which accounts for the autoinfestation in this helminthiasis

The embryonated eggs enter the host through the alimentary canal, reach the stoma and duodenum where the digestive secretions soften their walls, permitting the embry to escape, the embyos then grow in situ Without further migration they undergo moltings before reaching the adult stage with subsequent differentiation of the sexes

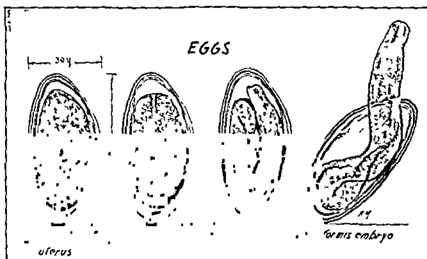


Fig 236—*Enterobius vermicularis* Various final stages in the development of the egg (Original)

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treatments by both methods 112 or 91 8 per cent were negative on post tre ment swab examinations In 104 cases there was no reaction to the treatme There were untoward effects in some cases such as nausea vomiting d rhea constipation headache dizziness lassitude and griping abdominal p but none were of a serious nature These investigators withhold treatm from individuals suffering from moderate or severe cardiac hepatic re and gastrointestinal disease Patients should abstain from alcohol dur the period of treatment

In the event that the patient is infested with *Ascaris lumbricoides* i advisable to attempt removal of the ascarids before administering the g tian violet treatment

Wright Brady and Bozicevich recommended for adults doses of 6 3 times daily before each meal for 8 consecutive days in series treatme should be repeated after a week's rest Children are given 1 cg daily each year of age

In 1940 in Cuba the excellent qualities of this drug were confirmed numerous cases of this parasitism It had been used since Wright and Bra presented their work in Havana at the Section on Parasitology of the Seve Medical Pan American Congress D'Antoni and Sawitz also confirmed t work

This medication does not require a special diet or previous purgatives a the patient may continue his accustomed manner of living and his usual cupation The drug is usually well tolerated except in a few rare cases which it causes vomiting and nausea In such cases medication must be d continued for a few days and later resumed with smaller doses over su a period of time as necessary to administer the total dose which is the sa in each case For children the dose is usually mixed with something sw and given in a dessert

PROPHYLAXIS

In all cases of enterobiasis it is good practice to examine all members the patient s family and to institute proper treatment at the same time of all the parasitized persons This prevents reinfestation of those who have be cured because it is possible for them to be reinfested by others who harb the parasite

Separate and treat all infested persons Brush the hands carefully wi soap and water taking care to brush the nails which should be cut sho All clothing must be washed in boiling water

The best prophylaxis and perhaps the only efficient means of preventi this infestation is mass treatment of all parasitized persons in famili nurseries asylums schools etc Prior to prophylactic treatment examine such persons including clinical exploration individual and collective as w as repeated microscopic examination of scrapings from the perianal regio When it is impossible to make such a survey impose collective treatment wh there is clinical evidence of infestation

causing violent pruritus inflammation leucorrhea and as a result of the undue scratching lesions are to be found in the clitoris and labia The parasites may migrate to the uterus and even reach the peritoneum through the Fallopian tubes causing inflammatory processes Certain cases of parasitic metritis are refractory to treatment Secretions are abundant and contain parasites and eggs

In cutaneous enterobiasis of the genitocrural groove which resembles intertrigo like eczema the parasites and their eggs are found in the epidermal lesions

The toxic action of the parasite produces urticaria and periodic spasmodic coryza

If the disease is not immediately treated it increases in severity the digestive disturbances become more aggravated nervous instability is augmented the system in general is greatly affected hence the patient suffers from lack of appetite becomes emaciated and finally anemic

DIAGNOSIS

The clinical diagnosis can be made presumptively from the presence of pruritus ani and intestinal disturbances but as a rule only by the finding of females or in rare instances of the eggs in the feces Frequently the parasite is discovered by the patient himself or in the case of children by the parents For laboratory diagnosis, use of anal swabs etc see Chapter 72

TREATMENT

(See also Chapter 64 for discussion of hexylresorcinol phenothiazine Lubisan Acranil)

Prior to the discovery of the parasiticidal action of gentian violet against *E vermicularis* reinfestation occurred quite frequently despite the complicated and repeated treatments which were used

The medicaments most commonly used were santonin calomel oil of chenopodium carbon tetrachloride tetrachloroethylene hexylresorcinol bismuth carbonate in large doses aluminum subacetate thymol phenothiazine and others Some have been used very frequently and without justification despite the interesting investigations of Wright Brady and Bozicevich (1938) relative to the efficacy of gentian violet in the treatment of enterobiasis

Gentian violet administered by the oral route has been used with excellent results This was suggested by W H Wright Chief Division of Zoology National Institutes of Health United States Public Health Service who made experimental observations on this question in collaboration with Brady and Bozicevich

Wright et al treated a total of 163 cases of enterobiasis with gentian violet Of these 163 cases 64 were adult and 99 were children under 16 years of age Many of the latter patients were 4 years or over Thirty six of the 163 cases were noncooperative 5 individuals could not complete treatment because of reactions caused by the drug Of 122 patients who completed their

2 The rhabditiform larva (first rhabditiform larva) increases in size The primitive genital organ becomes hypertrophic The larva undergoes one molting retaining the rhabditoid type of esophagus, then the genital organs appear, and the larva is transformed into either the male or the female adult form Copulation takes place, and the female becomes gravid, the eggs being embryonated in the uterus The female then lays eggs These eggs hatch freeing the rhabditiform larvae (second rhabditiform larvae) which are identical with the original or first rhabditiform larvae This second rhabditiform larva, born in the fecal substance, is transformed into a filariform larva by a mechanism similar to that previously described, and is the infestive form Thus the infestive form of the larva is formed either directly through transformation of the first rhabditiform larva or indirectly through transformation of the second rhabditiform larva, which in turn is a product of a sexual nonparasitic generation The former is called the short or direct cycle, the latter, the long or indirect cycle

When the infesting form comes in contact with the skin or mucous membrane, it penetrates deeply and migrates to the lungs, either by way of the circulatory system (Fulleborn) or of the connective tissue (Brumpt), regardless of which cycle of development the larva follows Upon reaching the lungs it travels up the respiratory tree to the larynx and into the pharynx It then goes down the esophagus, passes through the stomach, and finally reaches the duodenum where it changes into the adult parasitic, or strongyloid, form The fertilized female bores through the mucosa where it lays embryonated eggs These hatch and the rhabditiform larvae emerge The larvae are expelled during defecation and a new cycle begins

The habitat of the *strongyloid female, parasitic, or intestinal form* is the mucosa, not the lumen, of the small intestine This female measures 2 2 mm by 34 microns The anterior portion of the body is very thin, the posterior portion thickens and terminates in a conical tail Its integument has fine transverse striations The mouth has 4 very small lips

The *eggs* are ellipsoid, approximately 50 to 60 by 30 to 40 microns They have a very thin single colorless refractive wall They fill the uteri of the gravid female, those lying closer to the vulva becoming embryonated In fecal cultures, some of the eggs may burst, giving rise to rhabditiform larvae within the uterus of the rhabditoid female

DIFFERENCES BETWEEN THE RHABDITIFORM LARVAE OF STRONGYLOIDES STERCORALIS AND THOSE OF NECATOR AMERICANUS

Morphologic —

1 The rhabditiform larvae of Necator, just as it emerges from the egg is smaller than the rhabditiform larva of Strongyloides

2 The mouth of the rhabditiform larva of Strongyloides is shorter than the mouth of the rhabditiform larva of Necator

3 The rudiment of the genital organs of the rhabditiform larva of Strongyloides is much more developed and more clearly seen than the rudiment of the genital organs of the rhabditiform larva of Necator, which is barely perceptible and practically does not exist

4 There is also some difference in the esophageal bulb of the 2 rhabditiform larvae, the esophagus of the larva of Necator being relatively narrower and longer on the whole

Biological—Other data are related to the evolution of the larvae in coprocultures

1 The rhabditiform larva of Strongyloides develops rapidly, in its short cycle, and becomes a filariform larva, morphologically and structurally different from the filariform larva of Necator

2 The development, in coprocultures, of the characteristic sexual forms of Strongyloides permits us to make a diagnosis, because Necator has no sexual forms in coprocultures

3 Fresh feces in strongyloidiasis may contain rhabditiform larvae of Strongyloides but generally no eggs, while fresh feces in necatoriasis usually do not contain rhabditiform larvae of Necator but do contain the eggs In short, nonembryonated eggs in re

Strongyloidiasis

(Parasitism Produced by *Strongyloides Stercoralis*)

Synonym —Cochin China diarrhea

HISTORY

Strongyloides stercoralis was first observed in 1876 by Normand in the diarrheal feces of French soldiers of Cochin China Bavay described 2 different forms but it was Leuckart who, in 1884, proved that both forms belong to alternate generations of the same species Askanazy, in 1900, showed that the female invades the intestinal mucosa and there produces lesions Durme Looss, Ransom and Fulleborn described the mode of invasion skin, blood, lungs, trachea, pharynx, and the later migration into the intestine (1902 1904)

Kreis reported the male in 1932 It was believed until that year that development of the egg was by parthenogenesis Faust (1933 1935) made a detailed study of the development of the larva to the adult stage

GEOGRAPHIC DISTRIBUTION

Environmental conditions requisite for the development of *S stercoralis* are similar to those of Necator and Ancylostoma For this reason, coexistence of both parasites with Strongyloides is a frequent finding On the other hand, Strongyloides may develop at temperatures lower than the other two, therefore, it is much more widely distributed than the others, occurring in regions where Ancylostoma cannot survive While parasitism with this organism frequently occurs, nevertheless *S stercoralis* is found less frequently than all the other roundworms observed in Cuba.

CAUSATIVE AGENT

Strongyloides Stercoralis (Bavay, 1876) Stiles and Hassall, 1902

Synonyms —*Anguillula stercoralis* Bavay 1877, *Anguillula intestinalis* Bavay 1877, *Leptodera stercoralis* Cobbold 1879, *Leptodera intestinales* Cobbold 1879; *Pseudorhabditis stercoralis* Perroncito 1871, *Rhabdonema strongyloides* Leuckart 1883, *Rhabditis strongyloides* Leuckart 1883, *Strongyloides intestinalis* Grassi 1883, *Rhabdonema intestinalis* Blanchard 1885

The parasite has two adult forms and a rather complex cycle of development There are two types of larvae one rhabditiform, the other filariform Of the two adult forms, one is parasitic, localizing in the intestinal mucosa, particularly in the duodenum The non parasitic form grows in artificial fecal cultures through the evolution of the rhabditiform larva

The first adult form is called "strongyloid" because of the long cylindrical esophagus The second form is called "rhabditoid" because of the double bulbous shape of the esophagus

The first adult form has been shown by Faust to be diecious, that is, having both sexes

Life Cycle

The female parasite lays its eggs in the intestinal mucosa The eggs immediately burst and the rhabditiform larvae escape into the intestinal lumen, are expelled in the feces, and develop in the following fashion

1 The larva enlarges and elongates, the esophagus changes into the strongyloid type (long, cylindrical), the primitive genital organ narrows, the tail elongates and becomes bifid The parasite molts once, and the larva changes from the rhabditiform into the filariform type This is the infesting form

cently passed stools may be either Necator or Ancylostoma, but if these feces contain rhabditiform larvae, the larvae are those of *S stercoralis* The eggs of Necator in recently passed feces, are not embryonated, while those of Strongyloides are always embryonated in duodenal fluid obtained by intubation, or in diarrheal fecal material. Since (in Cuba) *N americanus* and *S stercoralis* are so frequently found together in the same patient, it is of paramount importance that the morphologic and biological differential characteristics be constantly kept in mind while making microscopic examinations of stools so as to determine whether one or both parasites are present.

HABITAT

The female *S stercoralis* localizes in the duodenal mucosa or the upper portion of the human jejunum Therefore, the larval forms and sometimes the embryonated eggs are frequently demonstrated through duodenal intubation even though examination of the feces has proved negative

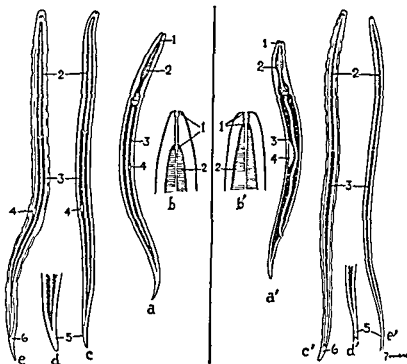
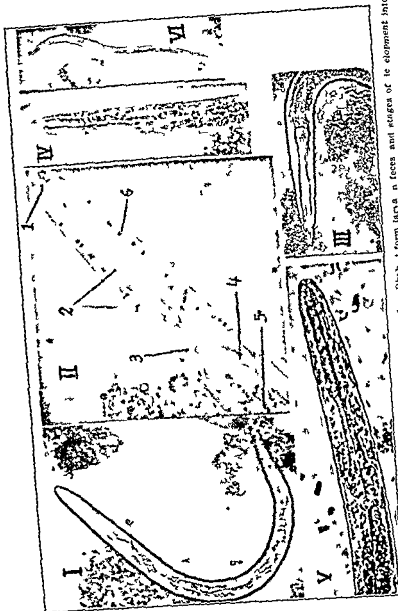


Fig 239 —*Strongyloides stercoralis* and *Necator americanus* larval forms. Rhabditiform ... end of the rhabditiform larva of ... -ricanus with d posterior ... er end. e Infective form ... *S stercoralis* (filariform ... liment of genital organ ... larva. (After Kouri and ... y of Editorial Profilaxis

Fulleborn reported eggs and females of this parasite in the trachea and in the lung tissue Faust has recovered both rhabditoid males and strongyloid females in the tracheae of experimentally infested dogs Larvae have also been found in a case of pleural hemorrhage (Froes), in the muscular coat of the colon (Yokogawa), and in the urine

The strongyloid species found in dogs and cats are morphologically identical with those found in man Fulleborn, Sandground, and Chandler



Rhab t form larva n feces and stages of le elopment into tl e fi arl

TREATMENT

For a long time *S stercoralis* resisted all known anthelminthic drugs It was not until gentian violet was introduced that the problem of treatment of this parasitosis successfully was solved

Thymol, male fern, oil of chenopodium, carbon tetrachloride, flowers of sulfur, emetine, and other medicaments have been used in strongyloidiasis by different authors with mediocre results

De Langen, in 1928, first proved the efficacy of gentian violet in this disease Faust in 1929, was the first to use it in the United States in 47 patients controlled by repeated coprologic examinations Forty five of these patients were completely cured of this parasitism In tropical America, Ceballos Carrión, in Guayaquil, Ecuador, in 1934 treated and cured 17 children with gentian violet

Kouri and Basnuevo, in 1935, successfully treated with gentian violet 8 patients who had had this parasitism for 4, 5, or 8 years and who had resisted all previous anthelminthic treatment Kouri, Sellek, and Rivera, in 1936, reported 7 cases of this parasitism in children treated and cured with this drug, controlling the treatment by counting the larvae before during, and after administration of the gentian violet Since then, all cases of strongyloidiasis at the Dispensary of the Institute of Tropical Medicine of the University of Havana have been successfully treated with gentian violet (Kouri, Basnuevo, and Sotolongo) Falla Alvarez and others have also reported cure of patients with this medication

Medicinal gentian violet (hexamethylene pararosaniline chloride) is used in 5 cg tablets given in doses of 3 tablets daily for adults (15 cg daily), 1 after each meal, for 20 consecutive days It may also be given in doses of 4 tablets daily (20 cg), before meals, for 15 consecutive days, with a total dose of 3 Gm , in a course of treatment which can be repeated, if necessary, after 7 to 10 days' rest

Older children are given the same dose as adults Younger children receive this drug in doses of 1 cg daily for each year of *apparent* age, as in enterobiasis, in divided daily doses, given before meals, for 20 *consecutive* days, in a course of treatment which can be repeated, if necessary, as with adults after a rest period of 7 to 10 days

D'Antoni, of the Department of Tropical Medicine of Tulane University, has shortened the length of treatment to 4 days, giving larger daily doses and increasing the dose progressively, with good tolerance, as follows

First day	6 cg , 3 times a day, or 18 cg daily
Second day	9 cg , 3 times a day, or 27 cg daily
Third day	12 cg , 3 times a day, or 36 cg daily
Fourth day	15 cg , 3 times a day, or 45 cg daily

The total dose in 4 days is 1 26 Gm , or 1 Gm and 26 cg administered in 4 days

In the United States, gentian violet is available in enteric coated tablets containing 0 01 and 0 5 Gm , respectively

In refractory cases, 25 c c of 1 per cent aqueous solution of *gentian violet* (25 cg) may be introduced directly into the duodenum with *satisfactory* results

believe that they are the same species Brumpt and others state that they belong to different species (*S canis S felis*)

Basnuevo and Kouri have found Strongyloides larvae in dogs They believe that this was the first time this parasite had ever been seen in dogs in Cuba Different species of Strongyloides infest different animals *S fulleborni* chimpanzees *S suum* hogs *S papillosus* sheep *S avium* chickens *S simiae* monkey

NUMBER AND LIFE SPAN

The number of parasites varies in different cases Usually the parasitism is mild or moderate Less frequently there are cases of massive parasitism in which larvae are abundant in the feces In Kouri s statistics only once have the eggs of the parasite been found in the stools of a patient with profuse diarrhea They can ordinarily be found by coproculture but these eggs come from free living females and not from the parasitic females Eggs of parasitic females are often found in fluids obtained by duodenal intubation enveloped in mucus The eggs contain embryos with active movements which rapidly cause the eggs to burst and free the rhabditiform larvae

The life span seems to be quite long judging by one case in an endemic zone (Leichtenstern) in which the feces showed larvae for 13 years

Patients in Havana have carried the parasite for nearly 10 years reinfection in Havana is difficult These cases have all been cured with gentian violet

Nevertheless if we agree with Thira Nishigori and Faust that internal reinfestation (hyperinfestation) is possible then the life span of the parasite is very difficult to determine

SYMPTOMATOLOGY

In severe parasitism local skin reactions such as urticaria violent pruritus papular eruption and edema may appear at the site of penetration Because of the irritation of the intestine disturbances such as hemorrhagic diarrhea may occur Anemia and eosinophilia may be observed

Migration of the larvae through the lungs may be accompanied by slight fever general malaise anorexia bronchial catarrh and other signs of pulmonary irritation on rare occasions by symptoms of mild bronchopneumonia

The general state might be affected in cases of severe or prolonged diarrheas with loss of weight weakness anorexia relatively mild anemia vertigo edema and tachycardia upon the slightest effort

Mild parasitism causes little disturbance In the tropics infestation by this parasite is frequently associated with necatoriasis ancylostomiasis and other helminthiases

DIAGNOSIS

Diagnosis is made by microscopic examination of the feces where the rhabditiform larvae are found If the feces remain without examination for some time after they have been passed the evolutionary forms may be found filariform larvae and even sexual forms Refer to Chapter 72 for details

HISTORY

This disease probably existed among the ancient Egyptians The clinical picture was described in Italy, Arabia, and Brazil long before Dubini in 1838 discovered the *Ancylostoma duodenale* It seems certain that a species of animal Ancylostoma had previously been described and given the name "hookworm" because of the radial appearance of the copulatory bursa of the male In 1842 Dubini gave the name *Ancylostoma duodenale* to the parasite found for the second time in human cases This parasite was assumed to be the same as that previously described in Egypt, to which the name Egyptian chlorosis had been given

In 1866, Wucherer found this parasite in patients who had died of tropical anemia in Brazil

In 1879, Grassi and Parona described the presence of eggs in the stools of patients with tropical anemia It was thought at that time that the disease was confined to tropical or subtropical zones, but this proved to be erroneous when some time later a case of anemia caused by Ancylostoma was reported to have originated in St Gothard's tunnel in Switzerland

Between 1877 and 1880 the etiology and diagnosis of hookworm disease were established, largely through the work of the Italian investigators, Grassi, Maggi, Pavesi, and the Parona brothers The symptoms and treatment were described by Concato, Perroncito Bozzolo, and Graziadei between 1879 and 1881 After the St Gothard tunnel was completed, the disease spread throughout the mining regions of Hungary, Germany, France, Holland, Belgium, Spain, England, and Sicily, carried by miners who had become infected in the St Gothard tunnel

Perroncito, 1880, was the first to discover the metamorphosis of the rhabditiform free living larva into the filariform infective larva, while the development of the adult worm in the intestine was first described by Leichtenstern in 1886

Penetration of the skin by the infective filariform larva of *Ancylostoma duodenale* was described in 1886 to 1897 in Egypt by Looss Following the accidental spilling of a culture of the larvae of this parasite on his hands, he noticed a local dermatitis with pruritus, and later was able to find eggs of the Ancylostoma in his stools He therefore concluded that he had become infected through the skin Looss, in 1911, while working with *A caninum* of dogs, showed experimentally the path followed by the infective larva from the skin to its usual habitat in the intestine, after having passed through the lungs, the trachea, and the glottis

The disease has been known in the southern part of the United States since 1845, but the parasite, *Necator americanus*, was not seen until 1893, and was not differentiated from the Old World species, *A duodenale*, until 1902, when Stiles, in studying specimens sent to him, recognized that he was dealing with a new species The specimens were sent by Smith and Clayton from the United States and later by Ashford from Puerto Rico Stiles first called the parasite *Uncinaria americana*, a name which he later changed to *Ancylostoma americanum* The name was finally changed to *Necator americanus*, by which it is known today

Many of the anemias in the southern parts of the United States, Puerto Rico, and Cuba were later attributed to this species In 1909, the Sanitary Commission of the Rockefeller Foundation was established to combat this disease, and since that time this organization has cooperated with the governments of various countries throughout the world in an effort to control this disease

Ashford was the first to describe the parasite as the cause of anemia in farmers of Puerto Rico On Nov 21, 1899, he sent the following telegram to the Chief Surgeon in San Juan, "Today I have proved the cause of the pernicious anemias in the Island, they are caused by *Ancylostoma duodenale* "

About 1 year and 6 months after the discovery by Ashford in Puerto Rico, Guitéras *(1901) reported the first case in Cuba, in a patient* who had come from the southern part of the United States Later the work of Agramonte, Guitéras, Plasencia, Entralgo, Lebredo, etc, contributed to the knowledge of the spread and distribution of this parasite in Cuba

This drug is usually well tolerated and does not require special diet or previous purgatives It has a mild irritative action on the intestinal mucosa and is a mild cardiac stimulant

In pulmonary infections and in cases of massive or old intestinal infestation, treatment may be given intravenously The patient receives while fasting and at bed rest, 0 5 per cent gentian violet in quantities not greater than 25 c c, by slow intravenous route This injection may be repeated on alternate days up to a total of 5 injections

Kouri has had considerable experience with intravenous injections of 0 5 per cent gentian violet in 5 c c ampules administered on alternate days for 2 consecutive months to patients with symptoms of lymphangitis chyluria and filarial hematochyluria (Kouri, Basnuevo, and Sotolongo) It was well tolerated and showed excellent clinical results Intravenous injections were also used by Olivier and Kandou in 1927 in the treatment of clonorchiasis Concentration of the aqueous solution of gentian violet should not exceed 0 5 per cent and not more than 25 c c should be administered at a time

Even though the larvae of Strongyloides still appear in the stools for a few days or weeks after treatment, experience has shown that the parasitic females may finally die (Craig and Faust)

PREVENTION

General Prophylaxis

General prophylactic measures are similar to those described for the other nematodiases

Man is the principal disseminator of this disease although cats and dogs harbor certain species of Strongyloides (*S canis* and *S felis*) which are biologically and morphologically indistinguishable from the Strongyloides which are parasitic to man

Individual Prophylaxis

As in hookworm disease protection of the skin especially of the hands and feet is necessary to prevent cutaneous penetration by the larvae from soil contaminated with excreta Entrance of the larvae through the mouth seldom occurs

DISEASES CAUSED BY WORMS BELONGING TO THE ORDER STRONGYLATA

Hookworm Disease

(Parasitism Produced by Hookworms *Necator Americanus* and *Ancylostoma Duodenale*)

Synonyms—(1) For *Necator americanus* infection necatoriasis, New World hookworm infection, American hookworm infection, American uncinariasis of certain texts (2) for *Ancylostoma duodenale* infections uncinariasis ancylostomiasis, Old World hookworm infection (3) for both hookworm infections in Egypt, Egyptian chlorosis, in the West Indies, edematous cachexia stomach ailment of the Negroes, heart trouble of the Negroes, in Brazil canconçao and opilação (pro parte) in tropical Africa, anemia or intertropical hypohemia, in Europe, anemia of miners, tileworkers, and tunnel workers

N americanus is a pinkish white round worm, frequently stained dark by digested blood The *male* is 7 to 9 by 0 3 mm, the *female*, 9 to 11 by 0 4 mm The body is cylindrical The posterior and anterior extremities of the female are thin, the posterior extremity of the male is broader because of the copulatory sac or bursa This species is smaller and thinner than *Ancylostoma duodenale* Males of *A duodenale* are 8 to 11 by 0 4 mm, the females are 10 to 18 by 0 6 mm

The position assumed by the Necator is very characteristic The body describes an arc, with the ventral surface on the inner side The anterior extremity curves back over the body so that the buccal capsule faces the convex dorsal surface The position of the body in the male is similar, but the curvature is greater

Ancylostoma shows an irregular curvature The cephalic end is straight or slightly curved, following the general curvature of the body

Table XXIII shows the differences between *N. americanus* and *A duodenale*

TABLE XXIII

	ANCYLOSTOMA DUODENALE	NECATOR AMERICANUS
Buccal capsule	Teeth, 2 on each side	No teeth, but lip like pouch formed plates
Distal end of female	A very fine sharp point or tail	No tail or point
Distal end of *male*	Spicules originating from the copulatory bursa, *diverging, and ending in a point*, the bursa is umbrella shaped	The spicules from the copulatory *bursa lie near the end*, close together, and bear a hooklet, the bursa looks as if it contains 2 lobes
Sexual orifice of female	*Lies behind the middle of the body*, on the convexity	*In front of the* middle of the body, on concavity
Position of body in rigor mortis	The head and, in the male, also the distal end are bent in from the ventral side of the body ("C" position)	The head and, in the male, also the distal end are bent from the dorsal side, almost hook shaped
Size	Somewhat larger and thicker than Necator	Somewhat shorter and more slender than Ancylostoma

The *eggs* of *N americanus* are ellipsoid, about 70 by 40 microns, longer than those of *A duodenale*, which are 60 by 40 microns The wall is very thin, colorless, and refractive

The egg is composed of a granular grayish substance divided into 4 to 8 cells or metameres (blastomeres) Each metamere has a clear rounded zone which represents the nucleus.

The eggs of Necator and Ancylostoma do not develop in the intestine because of the temperature, lack of oxygen, and the presence of inert gases In an external environment there are some factors which favor, others which arrest, development of the eggs

1 **Reaction of the Medium.**—Very alkaline, but particularly very acid, stools inhibit the development

2 **Chemical Conditions**—Oxygen favors, sea salts and sulfates arrest, the development The eggs can live for 28 days in feces in sewage

3 **Physical Conditions**—Optimum temperature is 25° to 30° C Humidity and darkness favor development of the egg

4. **Favorable Soil**—Certain soils favor development of eggs of Necator and Ancylostoma in warm climates, plantations, especially coffee, banana, and sugar cane, rubber, and cacao, in mild climates, brickyards and tile works, and in cold climates, mine pits, where the eggs find correct conditions for their growth In these media, the intraovular development of the embryo takes place in 24 hours, according to Chandler

GEOGRAPHIC DISTRIBUTION

Necator americanus predominates in the Western Hemisphere, Central and South Africa, southern Asia, the East Indies, Polynesia, Micronesia, and Australia, *Ancylostoma duodenale*, along the coastal regions of northern Africa, the Mediterranean, southern Europe, north India, China, and Japan Associated in small numbers with *N. americanus*, the latter can be found in south India, Burma, the Malayan Peninsula, central and southern China, the eastern part of the archipelago of the East Indies, Polynesia, Micronesia, Australia, Brazil, Paraguay, and Cuba

Hookworm can be found throughout the tropical and subtropical zones between 45° north and 30° south latitude, with the exception of *A duodenale*, which is seen farther north in the mining districts of Europe

N americanus is thought to have been introduced into the New World by Negro slaves and immigrants from Central and South Africa, while *A duodenale* was introduced, in small numbers, from the west, by Chinese laborers Soper, in Paraguay, in examining thousands of stools of patients under treatment, found Ancylostoma 13 times more frequently than Necator in regions where the European population was very small Maplestone in India found approximately 5 Ancylostomas for every 1 Necator In Cuba, *N americanus* is found in considerably larger numbers of cases than *A duodenale* (Lebredo more than 90 per cent, Kouri) In the few cases in which Ancylostoma is found, it is usually associated with Necator and has been seen in patients from the provinces of Pinar del Rio and of Oriente, and of the Isle of Pines (Kouri) *N. americanus* predominantes in Puerto Rico

Loughlin and Stoll (1948), in a report on hookworm infection in American servicemen with reference to the establishment of *A duodenale* in the southern United States, call at tention to one of their helminthologic features of World War II in the form of exposure of servicemen to infection with hookworm in areas infested with *A duodenale*, particularly in the Pacific Islands Reports of studies confirming this are gradually accumulating The in formation available to date, together with certain emphases arising from the further exam ination of data secured by American authorities on Navy and Marine personnel while on Guam, are brought together in this contribution to determine their relationship to the ques tion of the potential establishment of *A duodenale* in the United States They showed epi demiologic data concerning the probable establishment of *A duodenale* in the southern United States Of servicemen returning from the Pacific, 1 in 15 has been reported infected with this species of hookworm Also, analysis of hookworm infections carried by American service men from the South suggest a continuation into young adulthood (18 to 29 years) of faulty hygienic habits acquired in childhood The presence in returnees of these ages of a measur able incidence of *A duodenale* is thus combined with evident persistence of practices favor able for dissemination of hookworms The suspicion is thus increased that *A duodenale* has an opportunity to appear in areas of current hookworm infection Confirmation of such suspicion must await the discovery of the first instance of proved autochthonous infection, probably in one of the southern coastal states

CAUSATIVE AGENTS

The causative agents are *N americanus* and *A duodenale*

Necator Americanus (Stiles 1902) Stiles 1903 and Ancylostoma Duodenale (Dubini 1843) Creplin 1845

Synonyms —(1) For *Necator americanus* *Uncinaria americana*, Stiles 1902, *Ankylostoma americanum*, Verdun 1907, *Necator africanus*, Harris 1910, *Necator argentinus*, Parodi 1920, *Necator suillus*, Ackert and Payne 1922 (2) For *Ancylostoma duodenale* *Agchylostoma duodenale*, Dubini, 1843, *Strongylus quadridendatus*, von Siebold 1851, *Dochmius ankylostomum*, Molin 1860, *Sclerostoma duodenale*, Cobbold 1864, *Strongylus duodenalis* Schneider 1866, *Dochmius duodenalis*, Leuckart 1876, *Uncinaria duodenalis*, Railliet 1885, *Ankylostomum duodenale*, Lutz, 1885

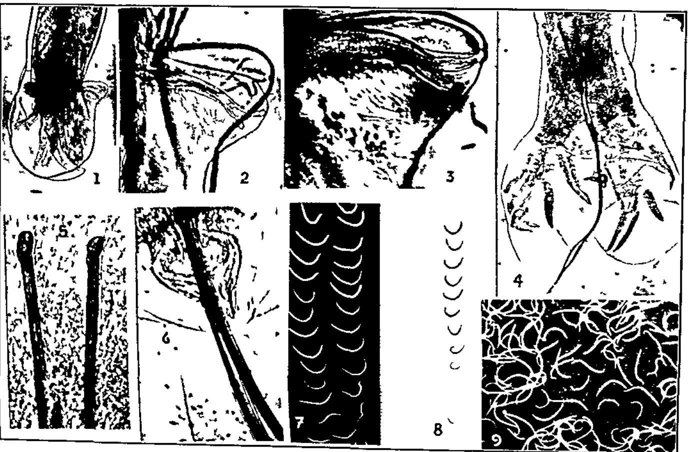


Fig. °41.—*Necator americanus* 1 Lateral view of copulatory bursa 2 two small lobes and two small posterior rays, lateral view 3 small bidigitate posterior ray extending into small posterior lobe 4 copulatory bursa, posterior view spicule and cloaca, rays 5 the 2 spicules at their origin 6 the spicules as they project through the cloaca 7 females, natural size 8 males, natural size 9 males and females, natural size. (Original photograph.)

When the eggs are ingested by coprophagous cockroaches *(Periplaneta americana)*, they are often destroyed, nevertheless, some continue their development when excreted by these insects Cockroaches, in this respect, are more useful than harmful to man The eggs remain viable in the digestive tract of chicks, which may disseminate the infection

Life Cycle

The egg is passed in the feces and undergoes a series of developmental changes giving rise to a *vermiform embryo* The embryo when hatched, becomes a rhabditiform larva, which molts, changing into a filariform larva

This second (filariform) larva again molts remaining enclosed in the old sheath This third or mature larva, the infesting form, is very active When it comes in contact with the skin of its host, it bores through, enters the circulatory system, and casts aside its old sheath The larva is then carried to the right side of the heart The heart pumps it into the capillaries of the lung, where the larva pierces the endothelium and invades the respiratory system From the alveolus it makes its way up through the smaller bronchioles, the larger bronchioles the bronchi, the trachea, the larynx, and then into the pharynx, reaches the digestive system and passes down the esophagus into the stomach, finally into the intestine In the intestine the larva molts for the third time, and now has a temporary buccal capsule



Fig 240 —*Above*, *Necator americanus* male and female (2 pairs) *Below*, *Ancylostoma duodenale* male and female (1 pair) (Original figure)

The larva molts once more and becomes a worm with a permanent buccal capsule In about 3 or 4 weeks, this worm develops into an adult male or female Copulation takes place, the female lays the eggs, and a new cycle is begun

BIOLOGIC CHARACTERISTICS OF THE INFESTIVE LARVAE OF NECATOR AMERICANUS

Resistance —The larvae may live 2 to 10 months in soil in plantations and mines, even though they do not ingest food They can live 18 months in water in the laboratory, which protects them from their natural enemies (Ackert)

Focus—The natural abode of the larvae is the soil in plantations upon which parasitized individuals have defecated

Distribution of the Larvae in the Soil—The larvae usually do not leave the place where they escape from the egg which has been deposited in human excreta

Tropism.—

Geotropism Infestive larvae leave the soil when the air is humid and warm because their thermotropism and hydrotropism are more intensive than is their geotropism. This causes them to climb up walls, trees, or any objects which touch the ground, if these objects are moist If the humidity of the atmosphere changes, and the air begins to dry, the larvae die because they cannot turn around to return to the moist ground Chandler, in the Indies, placed straw on the ground, the larvae rose to the surface of the straw when damp because of the morning dew, and then died when the straw dried in the afternoon sun

When the larvae climb, they ascend no higher than 30 cm For this reason, dark wells or latrines are to be abandoned when the level of the excreta reaches 20 to 30 cm below the ground

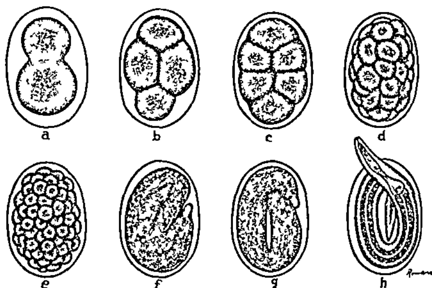


Fig 213 —*Necator americanus* Development of the egg *a*, *b* *c* Eggs with 2 4 and 6 metameres *d* beginning of the morula stage *e* morula in a more advanced stage *f* egg with tadpole like embryo *g* egg with vermiform embryo *h* egg with rhabditiform larva (Original drawing of Kouri and Basnuevo in Lecciones de Parasitologia y Medicina Tropical courtesy of Editorial Profilaxis S A Havana.)

Hydrotropism and Thermotropism Larvae show positive hydrotropism, which is utilized in diagnosis by coproculture This attraction for water *is still greater* if the temperature of the water is higher than the temperature of the environment, within certain limits (positive thermotropism) This thermotropism is intensely positive if the temperature of the water varies between 35° and 37° C

Some authors believe that thermotropism constitutes one of the determining factors in penetration of the skin by the larvae, because the temperature of the skin (36° C) is higher than that of the soil

Thigmotropism and Histotropism—Thigmotropism is the property of a living organism to react to contact with strange bodies, histotropism is the property of larvae to become attracted to and penetrate tissues Frequently the larva is indifferent in its selection of a host, and when it comes upon an animal that is not its habitual host, it may bore through the animal's skin and then die This indifference in the selection of a host may

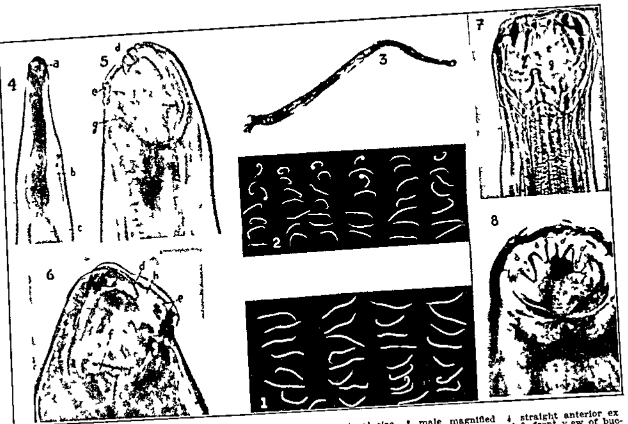


Fig 247—*Ancylostoma duodenale* *1* Females *2* males natural size *3* male magnified *4* straight anterior extremity *a* buccal capsule *b* esophagus *c* intestine *5* and *6* lateral view of buccal capsule *7* and *8* front view of buccal capsule *d* ventral hooklets *e* dorsal points *f* lateroventral pharyngeal plates *g* dorsal pharyngeal tooth, adherent to capsule *h* opening of buccal cavity *i* muscular pharynxes. (Original photographs)

Spontaneous disappearance of the hookworms is relatively rapid during the first 6 to 12 months greatly influencing the clinical symptoms of the disease (Chandler)

Resistance of the Patient —Children are less resistant to the infection and its clinical manifestations than are adults females less than males and whites less than Negroes

The nutritional state of the patient frequently constitutes the most important point in this problem Most patients suffering from severe anemias are undernourished and consequently have very poor resistance Numerous clinicians including Ashford Faust Rhoads Castle Payne Lawson and Kouri have found that a balanced diet to which liver and iron have been added can completely compensate for the loss of blood due to the hookworm even though the worms are not expelled

Reinfestation —In an endemic focus individuals are constantly exposed to reinfestation Thus new generations of worms are added to or replace those already present in the intestines Indubitably many patients develop considerable resistance to reinfestation (premunition) particularly those who are well nourished who have had an initial massive infection ' (Lorincz in Craig and Faust)

PATHOGENESIS

The injury from these parasites is caused by various mechanisms

Spoliative Action —Parasites to obtain nourishment extract blood and tissue from the individuals who harbor them Congestion and hemorrhage occur in the small lesions produced by the parasites stimulated by the anticoagulating toxin secreted by the worms Not only is blood lost from the constant sucking of the parasites but blood seeps from the wound which bleeds after the parasite moves to another part of the mucosa The powerful buccal capsule and musculature of the esophageal bulb are responsible for the large amount of blood that the parasites can withdraw

It has been estimated that about 0 67 c c (0 38 to 0 84 c c) of blood is extracted daily by each hookworm recently implanted in the intestine of man After several months or years *N americanus* does not extract more than 0 2 to 0 5 c c of blood daily If the quantity (0 67 c c) of blood extracted daily by a single parasite is multiplied by the thousands of worms which may be present and repeated day after day over a long period of time it is easy to understand the mechanism of the secondary anemias so frequently seen in hookworm disease

If parasitized individuals are well nourished and more important if liver extracts iron vitamins and animal proteins are administered in large enough quantities no anemia occurs because the parasitized patient can compensate for the daily loss of blood under this treatment Then too once the anemia is established no matter how severe it may be or how many worms are harbored it rapidly disappears upon administration of iron liver extracts and vitamins if the patient is kept on a balanced diet even though the parasites have not been removed (Rhoads Castle Payne and Lawson)

Traumatic and Bacterial Action —Traumatic action produces mainly small lesions in the intestinal mucosa produced by the parasite when it bores

be used to advantage in agronomical prophylaxis, a considerable number of infestive forms may be destroyed in this manner (Brumpt) Unfavorable animals used for destruction of these larvae are called animal "traps"—dogs, pigs, and other animals

According to Ackert, the larvae of Necator lose their power to penetrate tissues in 18 months, but they retain their positive thermotropism

The most economical method of destruction of the infestive form of Ancylostoma is to leave the excreta in the latrines and permit putrefactive gases to kill the infestive forms Sea salt, bichloride of mercury, Lysol, calcium chloride, formalin, etc, require prolonged contact with the larvae in order to kill them (Lambinet), but the cost of such chemicals is too great to justify their use, particularly since the results attained are quite dubious (Brumpt)

HABITAT, NUMBER, AND LIFE SPAN

N americanus and *A duodenale* live in the small intestine of man, especially in the upper portions Sometimes they ascend to the pyloric wall of the stomach, or descend to the cecum or even the ascending colon

Necator has been found in some species of African monkeys and in chimpanzees and pigs Experimental infection of puppies, cats, and Macacus has been carried out

It is not unusual for individuals to harbor as many as 200 to 400 worms, and, in infections with severe anemias, as many as 500 to 1,000 have been reported Smillie and Augustine reported a case with 3,000 Ancylostomas In Cuba 1 case was seen (Epifanio Dominguez) with nearly 2,000 Necators

According to Grassi and Parona, 1 000 Ancylostomas (500 males and 500 females) in the intestine correspond to 15,000 to 18,000 eggs per gram of feces Thus by multiplying the number of eggs contained in 1 drop of feces by 2, the approximate number of Ancylostomas harbored may be obtained

The life span of the parasite is probably 1 to 5 years

Pathogenic Role

The severity of the lesions and symptoms produced by *N americanus* or by *A duodenale* depends upon various factors, such as the number of worms, the course of infection, resistance of the host, and reinfestation

According to Darling, for each 12 worms there is a decrease of 1 per cent in the hemoglobin of the host Thus 240 worms will cause a 20 per cent reduction in hemoglobin, or, in other words, the hemoglobin will drop from 95 to 75 per cent, a thousand worms will reduce the hemoglobin to approximately 15 per cent

According to Smillie and Spencer, children who harbor less than 25 parasites do not show symptoms, with 26 to 100 parasites, they show hypochromemia with mild mental retardation, with more than 100 parasites they show severe disturbances arrest in development, retarded mental and sexual development, and severe anemia

Kouri has noted that individuals with more than 1,000 Necators usually show hemoglobin values as low as 12 to 15 per cent, less than 1,000,000 erythrocytes and generalized edema

At the onset of the anemia there ... of 15,000
meter, with great increase in
to normal or below normal, w
some months In severe cases there is usually total absence of eosinophiles

Rotter reported from the Pathological Institute of the Hospital de San Juan de Dios, San José, Costa Rica, a number of interesting histologic observations in fatal cases of ancylostomiasis There were hemorrhages due to the bites of the hookworms into the mucosa of the intestine These are very characteristic small submucosal hemorrhages in the center with a darker, pin point sized dot, indicating the size of the bite Microscopically, the tissue showed many extravasated red cells The hemorrhages sharply demarcate the muscularis from the mucosa The mucosa itself is practically free from blood There is some thickening of the submucosa with deposits of hemosiderin and scar forming connective tissue The submucosa is eight to ten times the normal thickness

There are chronic inflammatory changes in the mucosa in the neighborhood of the bleeding points In many cases polymorphonuclear neutrophiles accumulate around the area of hemorrhage, amounting almost to a phlegmonous condition The common picture seen in practically all cases of chronic ancylostomiasis is a marked thickening and sclerosis of the submucosa The connective tissue is rigid, often transformed into hyaline material Some small spots of hemorrhages are noted microscopically, which defy recognition with the naked eye The muscularis is very much thickened in all cases often fragmented and studded with cells The number of glands in the mucosa is decreased Eosinophilic cells are seen in large numbers

CLINICAL SYMPTOMS

Note the difference between the meaning of the terms "hookworm disease" and *hookworm infection* " *These are not synonyms Cases of infection* by Necator and Ancylostoma frequently occur without clinical signs or symptoms that is without causing clinically manifest disease, due to the fact that the presence of a small number of worms in the human intestine usually does not produce clinical manifestations and in certain cases individuals may harbor hundreds of the worms without apparent symptoms These symptoms depend upon various factors in addition to the number of worms the resistance and constitution of the host, food habits of the host, with either sufficient or insufficient amounts of the principal food elements, particularly proteins, iron, and vitamins

Skin—Penetration into the skin by the filariform larvae of *N americanus* frequently results in local pruriginous dermatitis, called "ground itch" or "dew itch," with edema, erythema, and papular or vesicular eruption which usually disappears spontaneously in approximately 2 weeks unless a secondary bacterial infection enters the abrasion, in which case more *advanced* lesions develop (Mazamorra in Cuba and Puerto Rico, Panighão in Brazil) *A duodenale* very rarely produces this dermatitis

Lungs—The infective larva, when migrating to the lungs and entering the capillary and alveolar endothelia causes microscopic trauma with small hemorrhages When the number of larvae migrating through the lungs is considerable, the lesions may be larger, with alveolar hemorrhage and round cell

through the mucosa or at times even the submucosa or aspiration, by means of the muscular esophagus, of a portion of the tissue into its buccal cavity This tissue first undergoes necrosis due to the toxins of the parasite is dislodged, and finally is loosened by the oral and pharyngeal portions of the powerful buccal capsule (work of Kouri on Ancylostoma of dogs)

The parasite ruptures the blood capillaries causing interstitial hemorrhages Areas of necrosis are observed around the cephalic pole of the parasite in dogs and also massive infiltration with leucocytes, especially polymorphonuclear neutrophiles and eosinophiles

Bacterial action is a result of traumatic action, in that the bacteria of the intestinal flora may enter the lesions and invade the tissues

Toxic Action—According to Smith and Loeg, Ancylostoma secretes an anticoagulating toxin, according to Alessandrini, also a hemolytic toxin According to *Weinberg Lebredo and Kouri, it also secretes a cytolytic and* histolytic toxin which softens and necrotizes the tissue

According to Lussana the urine of patients with anemia due to ancylostomiasis is toxic for rabbits which become anemic if injected with this urine The urine of these patients is not toxic after the Ancylosomas have been removed This does not however, prove that the anemia of patients with hookworm is due to the action of the secreted toxins, which may inhibit hematopoietic activity or cause hemolysis of red blood cells, or both, as some authors believe The anemia produced by hookworms cannot be of the hemolytic type since there is no decrease in red cell resistance to hypotonic salt solutions nor is there splenomegaly or reticulocytosis Neither is it of the aplastic type, since it is a secondary microcytic hypochromic anemia which readily responds to iron therapy

The rare cases of primary macrocytic hyperchromic anemia reported in hookworm disease may result from a predisposition of the patient or they may constitute anemias *sui generis* superimposed upon hookworm disease.

As stated above the anemia seems to be caused by chronic loss of blood frequently associated with an iron deficiency or a state of chronic malnutrition

PATHOLOGY

Alterations occur in the blood viscera and particularly the digestive tract In advanced stages of the disease the number of erythrocytes may be less than 1 000 000 and the hemoglobin content as low as 17 per cent or less However, there are cases of polycythemia and high hemoglobin due perhaps, to stimulation of the hematopoietic organs by *the hemotoxins absorbed* Usually eosinophilia is marked although in the last stages of the disease it may be mild or moderate or it may be absent

At autopsy, the cadaver does not appear emaciated The edematous condition exaggerates the adipose status The tissues are pale, the liver, heart, and kidneys show fatty degeneration, the serous cavities show effusions The duodenum and jejunum display a considerable number of minute wounds surrounded by small ecchymotic zones If an autopsy is performed within 3 hours after the death of the patient, the parasites can still be seen clinging to the walls of the intestines

swelling of the abdomen in the absence of helminthic infections such as *Ascaris lumbricoides* to which this physical sign is also attributed One should not forget that the classical picture of this disease in its severe stage was described before the clinical manifestations of malnutrition were known and that a great number of the symptoms seen in hookworm disease may be attributed to this because this disease presents combined symptoms of malnutrition and helminthic infection

Endocrine secretions may be diminished and puberty retarded in these cases The picture also shows edema weak pulse mental retardation apathy and even sexual impotence or sexual incontinence If treated inadequately the disease may terminate in complete physical exhaustion with cardiac insufficiency and anasarca occasionally resulting in death

During pregnancy *parasitized patients are predisposed to grave toxicosis* with albuminuria edema and diminished renal function According to Vickramasuriya hookworm disease during pregnancy is more serious than syphilis eclampsia or puerperal infection and plays an important role in fetal mortality

The correlation between advanced hookworm disease and nephrosis with edema albuminuria hypoproteinemia and hypocholesterinemia has been described by numerous authors (De Villeba Nébias Ponde and Garcia Carrillo) Suarez in 1933 in Puerto Rico found hypoproteinemia Porter in 1937 in chronic hookworm anemia found that there is compensation for the loss of *hemoglobin through an increased vital capacity of the lungs which is more* noticeable in people living in high altitudes There is also an increased tolerance of the tissues for lack of oxygen

The systolic pressure is notably lowered and the demand for a greater volume of circulating blood in the internal organs results in a low fluid content of the peripheral blood which is reflected in the intense paleness of the skin Cardiac hypertrophy is the natural sequel of prolonged hookworm anemia

DIAGNOSIS

The clinical diagnosis is relatively easy in those regions where this parasitic infestation occurs It may be confused with malarial cachexia or beriberi Confirmation of the diagnosis should be made by examination of the feces where the eggs are numerous In cases of mild infestation one must resort to coprocultures and concentration methods such as saturated solution of sodium chloride or Telemann s method See Chapter 72

PROGNOSIS

The prognosis is severe in the tropics especially in isolated regions where the diagnosis is delayed or never made In these regions the parasite is abundant and *is frequently associated with other intestinal parasites* and with malaria Septicemic complications of intestinal origin are frequent At times however in spite of all these apparently unfavorable factors even the most massive infestations if treated properly may be cured

infiltration causing difficulty in breathing These pneumonic lesions of the period of invasion of hookworm disease are not as frequent as in strongyloidiases and ascariases

Intestines and General Health—There are three stages in hookworm disease the initial or stage of invasion the chronic and the final or termination of the disease Based upon the severity of the symptoms the cases may be classified as mild without anemia moderate with appreciable anemia, and severe with severe anemia

In *mild cases* the anemia is insignificant and there are no clinical symptoms but the infected individual shows less resistance to intercurrent diseases These cases may be considered as simple carriers without clinical symptoms '

In the *second* or *moderate stage* blood loss is not restored by the host that is *the host shows moderate lack of blood regeneration* The symptoms consist of pyrosis flatulence abdominal fullness and epigastric pain which frequently disappear upon eating solid food or even upon ingestion of soil clay mud etc (geophagia) There may be a moderate intermittent fever lassitude and sometimes vasomotor disturbances dyspnea cardiac breathing and palpitation Poor food habits lead to malnutrition which unquestionably contributes to the development of this stage of the infection



Fig 244 —P[illegible] en ato s cacl c [illegible] Animas Hosp tal of Havana with severe [illegible] se eral lays later Generalized edema [illegible] more marke l on the right s le (Orig [illegible] nes de Paras tologia y Medicina Trop cal

The *third* or *severe stage* shows complete lack of compensation with the classical picture of hookworm disease There are constipation or diarrhea incomplete digestion of food and intensification of the symptoms described in the second stage of the disease The *skin is dry and rough, perspiration is diminished* the pale yellow appearance of the skin and mucosae is noticeable in individuals with white skin the hair is dry and lifeless edema of the face particularly of the eyelids and of the lower extremities is characteristic and contrasts with the emaciation of the rest of the body

A typical physical sign in children is the swelling of the abdomen which has been commonly referred to as potbelly ' in English and barrigones' in Spanish It should not be forgotten that a deficient diet is capable of causing

ment one or more times to obtain total eradication of the worms Hexyl resorcinol is administered when the patient is fasting in proper doses for adults and children after a saline purgative the preceding night The patient should continue to fast for 5 hours after the capsules have been taken and a saline purgative which some omit can be given 2 hours after taking the drug A light dinner the night before treatment and liquid food 5 hours after the medication are recommended

When administering carbon tetrachloride associated with chenopodium and tetrachloroethylene 3 c c in 27 c c of a purgative vehicle have the patient eat a light meal the night before treatment and take a saline purgative before going to bed

The drug should be given while the patient is fasting The patient should remain in bed and should receive liquid nourishment for the day As these two anthelminthics cause rapid purgative action usually no other purgative is necessary unless the desired results have not been obtained by the medicaments

If any of the anthelminthic treatments ingested cause excessive purgative action or if they cause dehydration with vomiting and frequent defecation the symptoms must be combated by the usual procedure hydrating the patient and even including venoclysis if necessary

Administration of calcium several days before treatment with carbon tetrachloride is a good procedure since as a rule there is hypocalcemia in hookworm disease as well as in intoxications by this drug

Alcohol is contraindicated during the treatment with carbon tetrachloride and tetrachloroethylene Carbon tetrachloride is contraindicated in alcoholism cardiac hepatic renal and pulmonary diseases The drug may be instilled directly into the duodenum by the Einhorn sound while the patient is fasting A few minutes after instillation if necessary 50 c c or more of a 33 per cent magnesium sulfate solution may be given

Hydroxylene is a combination of hexylresorcinol with tetrachloroethylene containing 0 10 Gm of the first and 0 3 c c of the second drug in each capsule in bottles of 10 capsules giving the total dose for adults Children are given one capsule for each year of age It is given in the morning while the patient is fasting using the same procedure as for the other anthelminthics In this combination suggested by Basnuevo in 1947 the combined actions of the two medicaments have proved advantageous effective and less toxic against hookworm Ascaris combinations and against each of these worms alone

EPIDEMIOLOGY

Although the skin is the usual site of entrance of the filariform infective larvae of hookworms infection by way of the mouth is possible if the infective form is ingested with food or drink and in such case development is usually direct without a period of migration within the host

Freezing and desiccation rapidly kill the eggs and larvae for which reason hookworm disease is endemic only in those tropical or subtropical areas

TREATMENT

1 **Treatment of Decompensation.**—In severe cases with intense anemia eneralized edema prostration and other symptoms the patients are kept in ed and given a balanced diet particularly rich in animal proteins with vita iins and mineral salts supplemented by iron and liver extracts orally or by njection Liver and iron are indispensable and give surprisingly good results Occasionally, *small* and repeated blood transfusions are necessary This treat nent should precede anthelminthic therapy so as to restore rapidly the pa ient s strength and blood loss and to balance the protein metabolism so that he anthelminthic therapy may be more easily tolerated

Moderate and mild cases may be given the anthelminthic treatment at nce

2 **Anthelminthic Treatment**—Of the anthelminthic medicaments carbon etrachloride tetrachloroethylene hexylresorcinol and oil of chenopodium ire the most effective Thymol chloroform beta naphthol extract of male ern and other drugs have also been used with variable results but at the present time the first four drugs are most generally used

Dosage Carbon tetrachloride and tetrachloroethylene are administered n doses of 3 c c for adults and 0 10 to 0 20 c c for each year of age for chil dren up to the age of 15 years Hexylresorcinol is given in doses of 1 Gm for adults and for children older than 10 years Oil of chenopodium is given in doses up to 1 5 c c for adults and 0 10 to 0 15 c c for each year of age for chil dren

Of these 4 medications the most effective for the removal of the hook worm is first carbon tetrachloride then tetrachloroethylene the latter being less toxic than the former Carbon tetrachloride is apparently more effective against *N americanus* than against *A duodenale* (Kouri) Hexylresorcinol is less effective but it has the advantage of being less toxic and of acting simultaneously against Ascaris and hookworms Oil of chenopodium is the most effective medication known against Ascaris being less effective against the hookworms but its toxicity is greater than the last two although if ad ministered properly it offers no danger for the patient

The combination of carbon tetrachloride (3 c c) with oil of chenopodium (1 5 c c) diluted in sufficient quantities as a purgative vehicle to make a total volume of 60 c c or distributed in 10 gelatin capsules has the advantage of acting simultaneously against Ascaris and hookworm so frequently associated in endemic areas In this way the grave accidents provoked by mobilization of the Ascaris can be prevented Carbon tetrachloride and tetrachloroethy lene in acting against these parasites neither kill nor numb them but make them more active producing obstruction or causing serious complications Chenopodium also heightens the action of carbon tetrachloride or tetrachloro ethylene

In mass treatment for ambulatory cases children the aged and de bilitated the drug of choice is hexylresorcinol because of its low degree of toxicity and ease of management although it is necessary to repeat the treat

one more often to hookworm infection than others Farmers and their families who cultivate the soil tile workers workers in brickyards and miners are exposed to hookworm infection *by their occupations because they often* work in complete absence of the most elementary sanitary facilities

Race—The white race is more susceptible than the Negro not only to hookworm infection but also to its consequences Thus the most intense infestations and the most severe clinical symptoms are often seen in whites rarely if ever in Negroes The percentage or incidence of hookworm infection has been found to be 10 times higher among whites than among Negroes in the state of Mississippi (Keller Leathers and Ricks)

PROPHYLAXIS

Individual prophylaxis consists in protecting the individual against the infective filariform larvae—shoes to be worn in infected areas and gloves in mines In the coffee growing regions of Brazil the percentage of infections was 9 times higher among barefooted laborers than among those wearing shoes, in certain rural districts children under 14 years of age were more intensely infected than older children (Smillie) When the children begin to wear shoes the incidence of infection decreases (Smillie and Augustine)

General prophylaxis consists in

1 **Treatment of Parasitized Individuals**—Individual treatment controlled by laboratory examinations may be sufficient in those regions in which the percentage of infection is low and environmental conditions are not favorable *for the development and survival of the larvae in the soil*

Mass treatment is recommended when the percentage of infestation is high, when there are no facilities for discovering parasitized individuals and where hygienic conditions are lax

These treatments lower the contamination of the soil and the chances of acquiring infection Unless mass treatment includes the entire population and is repeated at regular intervals and local sanitary conditions are improved the effects are only transitory (Scott and Barlow)

2 **Sanitary Disposal of Human Excreta**—In rural districts where sewers are impracticable, laws should be enacted to insure sanitary disposal of fecal matter, compelling construction of sanitary latrines and forbidding defecation on the ground The use of human fertilizer for vegetable gardens and plantations should be permitted only after chemical disinfection or storage for months in cement pits sealed against water There the eggs and larvae rapidly die

3 **General Education**—*Carrying out of sanitary measures* is surprisingly difficult since it is almost impossible to overcome the resistance of farmers to construction use and care of latrines even though these latrines are installed free of cost as is now being done by the Cuban government It is difficult to overcome the lifelong habits which some *peasants have of depositing* their excreta on the ground or to accustom them to use and take care of latrines Through general education by means of consultations and lectures on sanitary

in which the average precipitation reaches more than 50 inches yearly The customs and special habits of some countries particularly in the tropics and subtropics persistently maintain hookworm infection Farmers in Cuba and elsewhere for example are in the habit on plantations of passing their stools on the soil The areas are frequently dark and damp The optimum temperature of the summer months (28° to 32° C) and the rainfall make those places most appropriate for development of the eggs into larval forms In this manner foci of hookworm disease are formed on plantations and occasionally in the cellars of houses where children sometimes defecate and in other places where children play These conditions generally occur in the valleys of Central America and the Antilles In other regions (southern United States) foci exist in the damp sand on beaches In the cold regions of Europe infection occurs in the mine pits Since the infective filariform larvae usually do not leave the places in which they have developed unless carried away by rains only those individuals who frequently defecate in such places will be infected and reinfected especially if they wear no shoes This explains why hookworm disease in denser population centers is present frequently in high percentage and intensity while away from these foci or between focus and focus if it is found at all it is of a very mild degree

The custom of the Chinese of using human excreta as fertilizer for vegetable crops contributes to the persistent maintenance of a high incidence of hookworm among Chinese farmers If they store the excreta for some months later to be used as fertilizer in cement reservoirs the larvae rapidly die because of the lack of oxygen and the presence of other gases

Direct examination will not disclose mild infestations which are discovered by concentrating the eggs especially if the flotation method is used However none of these methods give adequate information as to the intensity of hookworm disease This information can be obtained by the methods of Stoll and Lane which give the number of eggs per gram of feces as a basis for calculation of the number of worms harbored by each individual and consequently the intensity of the infestation in any region (hookworm load)

Age—Infestation is more frequent between the ages of 13 and 19 years but occasionally maximum infestation may be found among younger children (who are more susceptible) although they are not exposed to infestation as often as are adults

There seems to be a certain degree of immunity against reinfection so that the first infestations progressively immunize man against future invasions

It has been proved that there is a gradual and spontaneous reduction in the number of hookworms if there is no reinfestation It has been estimated that there is a 90 per cent spontaneous reduction of *N americanus* and *A duodenale* within 1 or 2 years and total elimination after 5 or 7 years

Sex and Occupation—Infection is almost as frequent in males as in females although slightly higher in males due possibly to the fact that males are more likely to be exposed to infection It is the male who generally works the soil in tile works in mines etc It is known that certain occupations expose

narrower at the base The copulatory bursa is large and the rays are thick The terminal portions of the dorsal rays are quite sinuous The spicules are very long and delicate The eggs are similar to those of *A duodenale*

Creeping Eruption

Ancylostoma Braziliense Gómez de Faria 1910

Synonyms —*Ancylostoma ceylanicum* Looss 1911, *Agamonematodum migrans* Kirby Smith, Dove and White 1926 (larva)

This species was first discovered in 1910 by Gómez de Faria in dogs and cats in southern Brazil It was described by Looss, the following year, in a human case in Ceylon Since 1911 it has been reported several times in the intestine of man, dogs, and cats in Asia and on the American continent



Fig 246—Larva migrans Lesions on the internal surface of the right leg and knee.

In human cases it is usually a mild infection concomitant with *N americanus* In dogs and cats infected by this worm, it is usually seen in conjunction with the predominating parasite *A caninum*

The *male* parasite is 7 7 to 8 5 by 0 35 mm The *female* is 9 to 10 5 by 0 37 mm The buccal capsule differs from that of *A duodenale* in that the orifice is smaller, while each dental plate carries a small inner tooth, curved back, and one large lateral tooth The bursa

subjects with posters motion pictures and other means within the scope of their modest learning they should be taught how easily disease is propagated its enormous harm the danger of defecating on the ground and the necessity of using latrines This type of education is even more important than proper installation of latrines

Compulsory laws are less effective than instruction Instruction in sanitation should be given in homes schools clubs and elsewhere As a general rule human cooperation is easier through persuasion than by compulsion

We recommend that before and after establishment of a control program for hookworm disease the average incidence of infection (hookworm load) its extension degree of soil contamination and the environmental conditions be determined by surveys to establish more adequate prophylactic measures and to follow up the efficacy of these procedures

Fig 245 —Comparative study of the buccal capsules above and of the copulatory bursae below of the principal hookworms which parasitize man. (Redrawn from Looss 1911 in Belding Textbook of Clinical Parasitology New York, 1942 D Appleton Century Co by permission of the author and the publisher)

Ancylostoma Malayanum (Alessandrini 1905) Lane 1916

Synonym.—*Uncinaria malayana* Alessandrini 1905

This species was first described by Alessandrini in 1905 in the Malayan bear *(Ursus malayanus)* In 1916 Lane reported the same worm in the Himalayan bear *(Ursus troquatus)* Yorke and Maplestone in 19 6 found this worm in man

[illegible] tapered, and

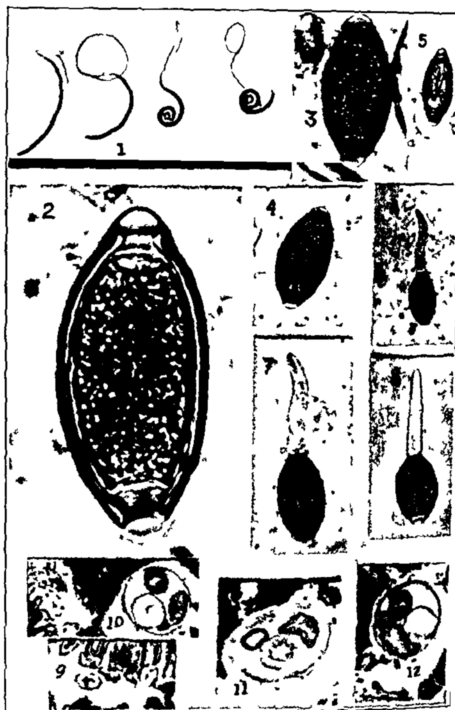


Fig 247.—*Trichuris trichiura* *1* *left* 2 females, *right* 2 males *2*, *3*, and *4* egg; *5* embryonated egg *6*, *7*, and *8* embryo emerging through one of the poles of the egg *9* stained histologic sections (*9* thin portion *10* to *12* thick portion) *of T. trichiura* in lumen of the appendix. (Kourí and collaborators From an article by J Alfonso.)

of the male is smaller, as wide as long, and the rays are short and plump The eggs resemble those of *A duodenale* Kirby Smith, Dove, and White (1925 to 1928) showed that the filari form infective larvae of this species are more frequently viable if they enter the host through the mouth than through the skin, and that the larvae which penetrate into the human body through the skin are responsible for the "creeping eruption" (larva migrans) seen in the southern part of the United States

Ancylostoma Caninum (Ercolani 1859) Hall 1913

Synonyms—*Sclerostomum caninum* Ercolani 1859, *Strongylus caninus* Ercolani 1859, *Uncinaria canina* (Ercolani 1859) Railliet 1900

This is the common Ancylostoma of dogs and cats Distribution is practically cosmo politan, but it is replaced in part, in tropical regions, by the species *A braziliense* It is doubtful whether it is a natural parasite of man, although it was once reported in a Filipino (Manalang, 1925)

The *male* is about 10 by 0 4 mm The *female* is 14 by 0 6 mm The buccal capsule is the widest and has the longest buccal orifice of all the species described in this genus Each of the 2 ventral dental plates bears 3 teeth the inner tooth being small and the outer large The copulatory bursa is large and supported by long, fine, typical rays The spicules are thick and relatively small The *eggs* are quite similar to those of *A duodenale* but are slightly larger They are 64 by 40 microns

The **life cycle** is similar to that of *A duodenale* Prenatal infection of dogs was dem onstrated by Foster in 1932 The canine and feline varieties are biologically different (Foster and Daengsvang, 1932)

The larvae of certain animal nematodes, especially *A braziliense* and *A caninum*, may occasionally bore through the human skin and live for a period of time in the skin where they creep or advance, giving rise to an extremely pruriginous dermatitis on that part of the surface of the skin which is covered by the larva in migration This condition is known as *larva migrans* or *creeping eruption* The original dermatitis may be complicated with pyo dermatitis and superficial ulcerations following violent scratching

Although the larvae of *A braziliense* are most often responsible, equally so are the larvae of *A caninum* and others

Infection occurs on beaches when the skin comes in contact with sand that has been contaminated by egg infested canine fecal material This con dition has been repeatedly reported in Cuba (Pardo Castello Braulio Saenz, etc) A patient of Kourí's showed 4 larva migrans in different parts of the thigh, buttocks, and knee

Intestinal infections by *A braziliense* have not as yet been reported in hu man beings in the southern United States, but in the coastal areas around the Gulf of Mexico, especially in Florida, and in eastern Texas, human cutaneous infection is relatively frequent It is caused by larvae of species of the canine or feline strains

The **treatment** consists in the local application, at the extremity of the area where the larva is found, of carbonic snow or ethylene chloride Sec ondary pus infections of the skin must also be treated

Prophylaxis consists in preventing contact of the skin with damp sand in endemic zones and in periodic treatment of ancylostomiasis of dogs and cats

embryo escapes forcing off one albuminous plug at the pole The free larva grows in situ until it becomes an adult form After copulation the fertilized eggs are passed in the feces and a new cycle begins

There is no autoinfestation with *T trichiura*

T trichiura is usually found clinging to the intestinal mucosa with the thin anterior portion buried beneath the epithelium It lies parallel to the mucosa In several cases it has been found deeply buried in the submucosa It is hematophagous

It usually localizes in the cecum and appendix of man rarely in other *parts of the colon and very rarely in the small intestine In massive infesta*tion the parasites can become implanted in the rectum Kouri has observed 3 cases of rectal prolapse in children in which a great number of Trichuris were found attached to the prolapsed and congested mucosa with the end portion of the parasite completely imbedded in the mucosa the parasite lying above and parallel to the mucosa

The *number of parasites* harbored is small from 1 to 10 although there are cases of intense parasitism where a thousand or more parasites are found

In 1930 Kouri found a case of a 6 year old girl who expelled after administration of 30 c c of milk of *Ficus glabrata* three bunches of Trichuris one of which contained 1 583 parasites of which 881 were females and 702 were males Moosebrugger reported a case with *900 Trichuris According to this author it is possible to calculate the approximate* number of Trichuris by estimating the number of eggs per gram of feces One gram of feces is rendered homogeneous in water and placed in a conical cup After a few minutes sedimentation 1 drop of the sediment is placed on a slide and covered with an 18 by 18 mm. cover glass and examined The number of eggs in 1 drop multiplied by 10 gives the approximate number of parasites

The *life span* of the Trichuris is unknown and is very difficult to calculate Premunition does not occur

The infestive form is the embryonated egg which is very resistant to adverse environmental conditions, this explains the frequency of parasitism with this worm since the opportunities for infestation are numerous in man (eating vegetables containing embryonated eggs or transferring the infection on contaminated fingers)

PATHOLOGY

Toxic Action—It has been pointed out that conditions similar to pernicious anemia in man have been produced in lower animals infected with large numbers of parasites Although cases of severe anemia caused by this parasite have been observed in man they are very rare in Cuba the principal cause of parasitic anemia in Cuba is *N americanus*

Eosinophilia is not very pronounced Guiart observed that the urticarial crisis disappears once the parasites are expelled

Traumatic Action—Trichuris has very slight traumatic effect upon the intestinal mucosa It does not produce ulcerative lesions *It is capable of* affecting the sympathetic nerve endings thus causing reflex phenomena of intestinal origin

DISEASES CAUSED BY WORMS BELONGING TO THE ORDER TRICHURATA

Trichuriasis or Whipworm Infection

(Parasitism Caused by *Trichuris Trichiura*)

Synonyms—Whipworm infection, trichocephaliasis

HISTORY

This parasite was first described by Linnaeus in 1771 In 1761 Roederer had classified it in the genus Trichuris Goeze in 1782 placed it in the genus Trichocephalus

GEOGRAPHIC DISTRIBUTION

Trichuris is a cosmopolitan parasite, but it is much more abundant in tropical countries where the high temperatures permit very rapid development of the eggs

It is the most common of all intestinal parasites in Cuba According to *Kouri*, *Calvó*, and Basnuevo (1938), *of* 7 246 coprologic examinations made in Cuba, 31 to 49 per cent showed this *parasite* The largest percentage is found in Consolación del Sur, province of *Pinar del Rio, with 64 76 per cent positive cases in more than 283 fecal examinations These* percentages would probably have been much higher had concentration methods *been used* and serial examinations made

According to Verdun 80 to 85 per cent of the miners of northern France showed eggs of this parasite in their fecal material In Paris according to Brumpt, Trichuris was found in the intestines of 30 out of 100 adults examined

CAUSATIVE AGENT

Trichuris Trichiura (Linnaeus 1771) Stiles, 1901

Synonyms.—*Ascaris trichiura* Linnaeus 1771, *Trichocephalus suis* Schrank 1788, *Trichocephalus apri* Gmelin 1790 *Trichocephalus dispar* Rudolphi 1802, *Mastigodes hominis* Zeder 1803, *Trichocephalus crenatus* Rudolphi 1809, *Trichocephalus trichiurus* Linnaeus (1771) Blanchard 1895

The female *Trichuris trichiura* is approximately 4 to 5 cm long *Its wide portion*, which is about half as long as the narrow, describes an arc, the concave side facing the ventral part of the body The male worm is smaller than the female, 3 to 4 cm long The thicker end is spirally coiled with the convex surface lying ventrally For further details, see Gradwohl and Kouri (1948)

These parasites are pink when alive The blood filled intestine may be seen through the transparent cuticle as a dark line which proves that this parasite is hematophagous The worms become white when placed in formalin

The *egg* is elongated and symmetrically narrowed at the poles It is approximately 50 by 25 *microns* It is brownish the intensity of color depending on the duration of its passage through the intestine The dark color is due to impregnation of the eggshell with bile The eggshell is thick and perforated at the poles Each orifice is closed by a refractive, hyaline, colorless albuminous plug, which permits the embryo to emerge The egg consists of finely granular protoplasm

Life Cycle

The adult parasites usually live in the cecum and appendix After fertilization the female lays eggs, which are expelled in the feces When environmental conditions are favorable, the embryo develops in about 3 or 4 weeks, but at low temperatures in 6 months to a year If the embryonated egg is ingested it reaches the intestine, and becomes softened The

trichiura, 5 or 1 33 per cent *A lumbricoides*, 1, or 0 27 per cent both *T trichiura* and *E vermicularis* 1 or 0 27 per cent Parasites were observed more frequently in the appendices of children than of adults and were more common in acute than in chronic cases

Mechanism of Appendicitis Due to Trichuris—Appendicitis caused by Trichuris may be due to two different mechanisms (1) irritation of the sympathetic nervous plexus provoking a pseudoappendicitis (Blanchard), (2) inoculation of pyogenic bacteria thus causing a true bacterial appendicitis resulting from the growth of the bacteria (Metschnikoff) In the case of parasitic pseudoappendicitis vermifuges may give good results provided they penetrate the appendix but in cases of true bacterial appendicitis these drugs would have to act not only as vermifuges but as antiseptics as well (Brumpt)

Method to Be Followed in Parasitic Appendicitis Which Is Not Acute—In chronic and even in subacute appendicitis when the surgeon has decided not to act immediately, the recommended method consists of treatment directed against the parasite (if it exists) If the symptoms or disorder provoked by the parasite disappear an unnecessary operation may be averted. Sometimes even after extirpation of the appendix, the parasitized patients continue to have the same symptoms, which do not disappear until the parasites have been expelled by proper treatment In acute or subacute appendicitis in which prompt intervention is decided upon by the surgeon operation is necessary even if the origin is parasitic In Cuba, where parasitism is so frequent, one should systematically bear in mind the possibility of a parasitic etiology in appendicitis so that prompt surgical action may be taken All surgically removed appendices should be systematically examined for parasites in the laboratory so that in positive cases proper treatment may be instituted In this way recurrences after appendectomy may be avoided in some cases

DIAGNOSIS

Accurate diagnosis can be made only by thorough microscopic examination of the feces The presence of the characteristic egg is sufficient evidence See Chapter 72

TREATMENT

Most of the anthelminthics which have been used are for the greater part *without any specific action* *Thymol oil of chenopodium* extracts of various species of Ficus *(glabrata laurifolia doliaria) (leche de higuéron* see Chapter 64) and of the fruit of the papaya tree have been successfully used especially the last two Usually several treatments are necessary to effect a complete cure Oral administration of pentavalent arsenic compounds reduces the number of parasites in the intestines (Kouri et al) A series of such treatments may effect a total or almost complete cure Ferric ammonium citrate in large doses given over a long period of time has been used recently

Iron sulfate the juice of *Bromelia pinguin* (rat pineapple), and coconut oil *(Cocos nucifera*, L) have also been used

Infectious or Bacterial Action—Although this parasite may be capable of aiding bacteria of the intestinal flora to gain entrance into the body of the host some authors without experimental evidence have exaggerated its role in the transfer of typhoid fever cholera and dysentery

Inflammatory Action—Inflammatory reactions have been observed around the body of the parasite in the intestinal wall due possibly to pyogenic bacteria in the tissues (Weinberg and Joyeux)

SYMPTOMS

When the parasitism is mild it may go unnoticed since no definite symptoms are present but in massive infestation nervous and digestive disorders as well as inflammatory processes in the appendix may be produced

Nervous Disorders—When nervous disorders are present they are somewhat similar to those of ascariasis and other worm diseases They disappear when the parasites are expelled

Digestive Disorders—When the number of parasites is very large they may cause digestive disorders consisting of diarrhea abdominal pain and tenesmus simulating a dysenteric syndrome or they may even cause a true dysenteric picture Sometimes they are accompanied by muscle guard and upon pressure of spontaneous pains in the cecum

One case of chronic enteritis and fatal anemia due to Trichocephalus was reported in 1895 by Moosebrugger In Cuba severe anemia attributed to Trichuris has never been found even in cases of patients who harbored more than 1 000 parasites

Appendicitis Due to Trichuris

According to Blanchard *T trichiura* was first discovered in the appendix of man by Morgagni In Paris of 800 appendices of adults examined at autopsy by Brumpt about 4 per cent of the appendices and 70 per cent of the cecums contained this parasite Brumpt recommended that a careful investigation of these organs be made not only at autopsy where the parasites are frequently overlooked but also in the parasitologic laboratory

Lejars (1897) Guinard (1900) Girard (1901) and Menetrier (1909) reported Trichuris in appendices Metschnikoff was the first to call attention to this problem In 1901 he reported that by the use of the anthelminthics he had cured 3 cases of apparent appendicitis He recommended frequent administration of vermifuges and believed that the frequency of appendicitis is due to abandonment of this method of treatment Since that time Guiart has treated appendicitis with thymol *

In Cuba the frequency of Trichuris has been reported by Calvo in surgically removed appendices in the Municipal Hospital of Havana Three hundred and seventy five appendices were examined 20 or 5 33 *per cent* contained worms classified as follows *E vermicularis* 15 or 4 *per cent* *T*

*Editor's note These findings are not borne out by the American study of all surgical tissues removed in the operating rooms in the United States

weight as a total dose distributed over 10 days The patient should be watched closely and treatment should be discontinued at the slightest sign of arsenic intoxication

Kouri and his co workers submitted all these medications to rigorous control and found that Pentarsenol is the most efficacious antitrichuric medication (Kouri Basnuevo Amido Sotolongo and others) but it cannot be stated that this drug is specific against Trichuris A specific antiparasitic medication is one which will lead to the expulsion of 90 to 100 per cent of the parasites during the first treatment in 90 to 100 per cent of the cases treated

Absence of Trichuris eggs from the stools after treatment does not necessarily prove complete cure of the parasitism since it is known that negative phases exist in mild infestations Nor does the persistence of the eggs in the excreta after treatment necessarily mean that the drug is ineffective because if the eggs have not been counted one cannot ascertain whether or not the number of parasites has decreased or how much the decrease has been Counting the parasites expelled during treatment however gives an index of the efficacy of the drug used

PROPHYLAXIS

Prophylaxis is similar to that directed against A *lumbricoides*

General prophylaxis consists in (1) education of the public (2) use of latrines (3) avoidance of usage of human fertilizer, (4) discovering the focus of infestation by means of coprologic surveys (5) treating parasitized individuals

Individual prophylaxis consists in avoiding ingestion of embryonated eggs *in food by (1) filtration or boiling of water (2) washing all vegetables* well with water which is not contaminated or which has been boiled refraining from eating raw vegetables coming from foci of infestation (3) protection against flies, (4) washing the hands before eating

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Our experience in treating infestations by Trichuris one of the most frequent and refractory intestinal parasites in Cuba shows that in such cases most medicaments are valueless In some cases treated with the latex of *Carica papaya* (Papaya) and particularly with the latex of *Ficus glabrata (leche de higueron)* Kouri has succeeded in causing expulsion of hundreds and thousands of Trichuris in cases of intense parasitism This trichurifugal or trichuricidal action of *Ficus glabrata* is not constant so that a total and definitive cure is not always obtained

Robbins isolated the active principle from the latex of *Ficus glabrata* which he called Ficin

Thymol —Thymol has been used in some refractory cases In finely pulverized form it is given in 3 one gram capsules daily for 3 consecutive days at 1 hour intervals as recommended by Guiart The number of eggs found in the feces has been known to decrease with this treatment but complete cure is lacking after one treatment When thymol is administered patients should be warned against drinking any of the solvents of this drug—alcohol chloroform ether—against eating fats etc while under treatment because absorption of thymol is extremely dangerous even fatal in some cases

Oil of Chenopodium —Oil of chenopodium obtained by distillation of the plant commonly known as Apazote Pazote Mexican tea etc *(Chenopodium ambrosioides* var *anthelminthica)* is very efficient in its action against Trichuris although it is not a specific It acts through its active principle Ascaridol The dose is 1 to 3 drops for each year of age in children and up to 1 5 c c for adults mixed with 30 to 60 c c of castor oil as a purgative This drug is toxic if given in doses greater than prescribed here

Ferric Ammonium Citrate —Ferric ammonium citrate in large doses has been used in Cuba in the treatment of trichuriasis Kouri has concluded that it is beneficial in its action on the patient acting as a tonic and increasing the patient s strength and weight red count and hemoglobin It cannot be stated however that it has any direct action upon Trichuris Patients recover clinically and the number of eggs diminishes but a total and definitive cure is not obtained

Ferric ammonium citrate is administered in doses of 15 to 20 Gm daily for adults and 1 Gm daily for each year of age for children for a period of 10 or more consecutive days (This dose exceeds the usual 2 to 3 Gm given daily in the U S A and by British physicians —O F) In cases of colic or diarrhea the dose is decreased or powdered ferric ammonium citrate is given with powdered leaves of belladonna bismuth subcarbonate and kaolin The feces become dark or black

Pentavalent Arsenicals —Cases of refractory trichuriasis have led to the use of all types of antiparasitic drugs Since 1933 Kouri has used the sodium salt of oxy acetyl amino phenyl arsonic acid (Pentarsenol) administered orally 1 to 3 or 4 tablets of 0 25 Gm each given daily to adults and ½ to 2 tablets of 0 05 Gm to children at the rate of 0 07 Gm per kilogram of body

nematodes, and apparently cannot withstand the movements of the intestinal contents Within or partially penetrating the mucosa, the developing larvae grow to maturity and mate after passing through a series of molts (Bugge, 1934, Kreis, 1937, Weller, 1943) By the second to third day, the female possesses an egg laden uterus, copulation probably occurring about the end of the second day and even before molting is completed On about the fifth day and thereafter, embryos may be seen in the anterior portion of the uterus

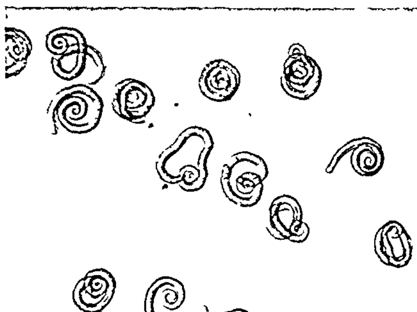


Fig 248 —Infective *Trichinella spiralis* larvae obtained by peptic digestion of muscle.



Fig 249 Fig 250

Fig 249 —Adult female *Trichinella spiralis* from the intestine of an infected animal *Note the uterus laden with eggs and embryos*

Fig 250 —Adult male *Trichinella spiralis* from the intestine of an infected animal *Note* the posterior terminal papillae

The mature female measures usually from 3 to 4 mm in length, by 0 060 to 0 072 mm in greatest width Considerable variations in the size of females may be observed, however, some forms being smaller and some greatly exceeding these measurements Males of *T spiralis* are more equal in size, usually from 1 4 to 1 6 mm long by 0 033 to 0 040 mm in

CHAPTER 38

TRICHINOSIS

IRVING RAPPAPORT

Trichinosis also known as trichiniasis and trichinelliasis, is a parasitic disease caused by the nematode, *Trichinella spiralis* *T spiralis* is classified by Chitwood and Chitwood (1937) as an aphasmidian nematode in the order Enoplida, suborder Dorylaimina, superfamily Trichuroidea *T spiralis* and *Trichuris trichiura* have morphologic similarities *T. spiralis* is the only species of the genus *Trichinella* It is capable of parasitizing almost every species of mammal, to a slight degree birds and is one of the few nematodes which completes its entire life cycle in the same host

HISTORY

The cysts of *T spiralis* were first reported by Tiedemann in 1822 and later by Hilton in 1833, and others The larvae of the parasite were first seen by Paget in 1835 in the muscles of a cadaver The organism was described and named *Trichina spiralis* by Owen in the same year, but the genus was later renamed *Trichinella* by Railliet in 1895, owing to the priority held by a genus of diptera of the same name The terms "trichina," "trichinosis," and "trichiniasis" still persist

Zenker (1860) was the first to demonstrate the pathogenicity of the parasite

It is probable that many acute cases of the disease and even epidemics occurred prior to 1860, but they were most likely regarded as typhoid fever or botulism Within the next five years, two severe epidemics occurred in Germany (Rupprecht, 1864, Kratz, 1866) In the one at Hettstadt there was a mortality of 16 per cent In the 1865 epidemic of Hedersleben, total population 2,000, 337 people became ill and 101 died The latter epidemic was caused by a single butcher who noticed an abnormal appearance of the meat of a hog and had therefore mixed it with that of two healthy animals He confessed to this adulteration shortly before his own death resulting from eating the same pork (Anonymous, 1866) These epidemics established trichinosis as an important public health problem For many years thereafter, countries accused one another of exporting infected pork

LIFE CYCLE AND MORPHOLOGY OF TRICHINELLA SPIRALIS

It is difficult to credit any single individual with the discovery of the entire life cycle of *T spiralis* It may be said that, through the combined contributions of the investigators mentioned above and others, the more important stages in the life history were expounded More intricate phases of the development of the parasite are continuously being reported

When a lower animal or man ingests raw or insufficiently cooked muscle containing infective larvae, the latter are liberated in the stomach and small intestine by the action of digestive juices on the muscle and cysts The mature excysted larvae measure 0.9 to 1.28 by 0.035 to 0.04 mm in the greatest width In vitro in the cold, these larvae are coiled, but on warming they become motile by uncoiling themselves and waving their extremities about in a whip like manner

Within 5 hours after feeding meat to an animal, the larvae burrow into the crypts of Lieberkuhn or under the epithelium of the intestinal mucosa They do not remain in the lumen of the small intestine since they do not possess organs for attachment as do many other



Fig 251 —Adult female *Trichinella spiralis* between the villi and penetrating the intestinal mucosa of a mouse Original photomicrograph (From Nauss Medical Parasitology and Zoology courtesy of Paul B Hoeber Inc)



Fig 252 —Section of heart muscle of a mouse showing a larva within a venule Original photomicrograph (From Nauss Medical Parasitology and Zoology courtesy of Paul B. Hoeber Inc.)

greatest width The sexes can easily be distinguished morphologically The female is larger The esophagus as indicated by the dark stichocytes or esophageal gland cells, occupies the narrowed anterior two fifths of the body, the uterus almost fills the posterior three fifths and is laden with eggs and embryos, the vulva is situated anterior to the uterus in the posterior part of the esophageal region, the posterior part is broad, smooth, and rounded The male is much smaller The narrow esophageal region extends through almost the entire anterior half of the body, the testis is finely granular, the posterior end of the worm terminates in two conical papillae which are very conspicuous

The adult apparently feeds on plasma and cell fluid which are probably obtained by means of the piercing action of a minute buccal stylet

Many textbooks on general parasitology state that the male disappears from the intestine soon after fertilization of the female Many reports in the literature, however, do not uphold this view Rappaport (1943b) found that in mice there was considerable regularity in the longevity and sex ratios, particularly in those animals infected with a dose of larvae bordering on the lethal On the whole, the ratios of males to females during the first 2 weeks of infection varied from 2 3 to 1 2 and the total number of adults in the intestine remained relatively constant After the sixteenth or eighteenth day, however, the females were eliminated from the intestine more readily than the males and to such a degree that there was a reversal of the sex ratio in favor of the males In some instances, the reversal was so complete that males were found to the exclusion of females in the small intestine after the third week During the fourth week the majority of the males also were eliminated Adults were not observed later than 54 days after infection In larger experimental animals, it appears that the longevity of the adults seems to depend upon the host species In man Zenker (1860) found male and female *T spiralis* 38 days after infection, Cohnheim (1865), after 50 days, Kratz (1866), after 8 and 12 weeks, and Carter (1949) 115 days after onset of symptoms

Both males and females penetrate the intestinal mucosa (Graham, 1897) The males are found only superficially under the epithelium, but the females burrow deeply, as far as the muscularis mucosae which seems to act as a barrier (Askanazy, 1894, 1895) Most investigators agree that the female worms deposit their young in the mucosa, thus enabling the larvae to migrate via the lymphatic system into the blood stream At the time the young larvae are laid they measure 0 09 to 0 12 mm by about 0 006 mm From the blood stream the larvae have been found to pass into almost every organ of the body Thus the symptomatology of the disease during this migratory phase is almost unlimited The larvae develop and encyst, however, only in voluntary striated muscle In organs other than voluntary muscle, larvae either degenerate and set up an inflammatory reaction in the region parasitized or else pass into the body cavities where they degenerate (Graham, 1897) Matoff (1940) has expressed the view that most of the larvae in organs other than voluntary muscle migrate into the body cavities but do not necessarily degenerate Instead, they may regain entrance into the circulatory system If this is true, the majority of the larvae finally make their way to the voluntary musculature where they encyst Matoff in this manner explained the reason for the extensive muscle involvement in the disease Graham gave a good explanation for the finding of more larvae in the musculature than in other organs He supposed that since the capillaries of the muscles are the smallest in the body, the larvae should find their exit there more readily He gave the dimensions of muscle capillaries as 0 005 to 0 006 mm in diameter and the



Fig 255 —*Trichinella spiralis* larvae in heart muscle of a mouse Note the extensive degeneration of cardiac muscle fibers with very little cellular infiltration This pathology is still a little too early to show the leucocytic infiltration which is so often found



Fig 256 —Early invasion of voluntary muscle fibers by *Trichinella spiralis* in a mouse Note the distribution of the early cellular reaction

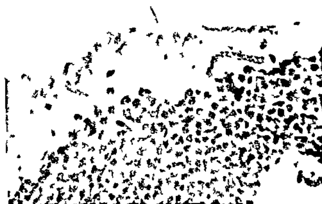


Fig 253.—*Trichinella spiralis* larvae in the marginal sinus of a mediastinal lymph node of a mouse. These larvae probably reached this organ via the circulatory system.



Fig 254.—*Trichinella spiralis* larva in heart muscle of a mouse. Note the very early degeneration of the cardiac muscle fibers adjacent to the parasite.

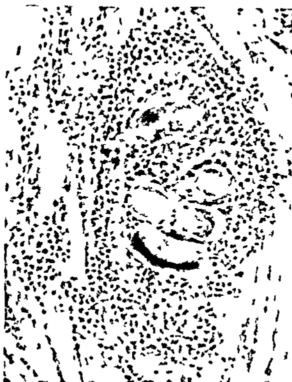


Fig 259 —Section of voluntary muscle of an animal showing a *Trichinella spiralis* larva *undergoing degeneration It is believed that this occurs when the sarcolemma of a newly* parasitized muscle fiber is not sufficiently resistant to the cellular infiltration

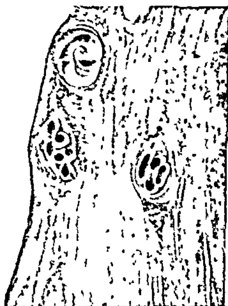


Fig 260 —Section of voluntary muscle showing old *Trichinella spiralis* cysts The animal was infected 18 months previously Note the thickness of the cyst walls, the fatty infiltration at the pole of one of the cysts and the reduction in cellular reaction as compared with Fig 258 Original photomicrograph (From Nauss Medical Parasitology and Zoology courtesy of Paul B Hoeber Inc)

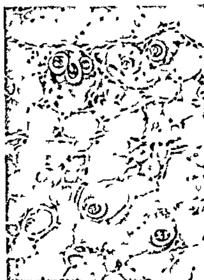


Fig 257 —Cross section of the same muscle as shown in Fig 256 Note the extensive swelling and degeneration of the affected muscle fibers



Fig 258 —Early encystment of *Trichinella spiralis* larvae in voluntary muscle of an infected animal Note the appearance of the cyst walls the early closure of the cysts 2 parasites within a single cyst and the extensive cellular reaction around the cysts Original photomicrograph (From Nauss Medical Parasitology and Zoology courtesy of Paul B. Hoeber Inc)

As in the discussion of the life cycle, the pathology and symptomatology of the disease may be considered under the 3 phases of the disease *intestinal*, *migratory*, and *musculocystic* Some workers (Rupprecht, 1864) prefer to include the early muscular phase with the migratory phase For reasons stated below, the author feels that his classification is more applicable for a better understanding of the disease Kratz (1866) believed that separation into phases may be confusing since all 3 phases may overlap

Intestinal Phase

The intestinal phase lasts as long as adult *T spiralis* remain in the intestine and begins shortly after ingestion of infective larvae The pathology may vary from a mere increased activity of the goblet cells to desquamation of the mucosal epithelium with superficial necrosis of the ends of the villi (Askanazy, 1895) In fatal cases occurring early and during the height of this phase, the destruction of the mucosa may be so severe that the glandular texture is obliterated, such early fatalities are, however, rare In intensive infections, there is often a round cell infiltration of the mucosa and submucosa usually in rows or in round perivascular patches Seldom are neutrophile found in appreciable numbers Most workers believe that it is in the mucosa of the intestine and in the lumen of the central lacteal of a villus that the larvae are deposited by a female and rarely, if ever, in the lumen of the intestine The muscularis mucosae appears in most instances to be the limiting border of the invading female worm

The majority of patients ill with trichinosis show some intestinal symptoms which may occur within a few hours after consuming infected meat and may last a month or longer These symptoms occur most commonly during the first week of infection last for 1 or 2 weeks and are usually of a gastrointestinal nature Diarrhea is the most prevalent symptom, resulting probably, from the intestinal catarrh Stools in such cases may be pea soup like as in typhoid fever or liquid as in cholera Other symptoms may include abdominal aches constipation, belching bloating, nausea and vomiting, loss of appetite bad breath, coating of tongue headache, low grade fever, dizziness general weakness and even prostration *Diagnosis is difficult and may be* confused with other gastrointestinal disturbances

Rupprecht (1864) and Kratz (1866) reported a peculiar muscular weakness or mild paralysis which began during the early part of the intestinal phase It is possible that this condition may have been caused by an intestinal toxemia or by the early stages of larval migration into the muscles

Migratory Phase

The migratory phase is a very important one In most instances, the physician is consulted some time during this period The migratory phase begins with the deposition of larvae by the adult females in the intestine as early as the fifth day of infection and may last as long as 11 or 12 weeks

larvae as 0.005 mm (0.006 to 0.007 mm according to Hemmert Halswick and Bugge, 1934). He also presented sections to illustrate the view that larvae may be forced out of the capillaries owing to the static pressure of the blood behind them, this pressure probably being increased by muscle contraction.

The greatest deposition of larvae occurs over a period of 6 days in rats (Levin, 1941) and 4 to 8 days in mice (Rappaport, 1943b). This deposition occurs early, beginning about the sixth day of infection, and corresponds closely to the longevity of the females in the small intestine. In man the deposition of larvae probably occurs over a much longer period of time owing to the longer life span of the female *T. spiralis*. The number of larvae that a single female deposits has been variously estimated to be from 10 to 15,000 (Matoff and Wapzarowa, 1937). It must be considered, however, that an accurate answer to this question is almost impossible to determine since many larvae are probably destroyed during the migratory stage and even in the musculature. In addition, resistance of the host, size of the initial dose of larvae, immunity and other factors probably play a large role in determining the number of larvae deposited and the number actually reaching encystment.

In the muscles, the larvae penetrate the individual muscle fibers and grow at the expense of the protoplasm. The sarcolemma becomes thickened and a cyst wall is formed about the larva, which by this time has become coiled. Encystment may be said to begin immediately upon entrance of a larva int a muscle fiber although the cyst wall does not become closed at the poles unt about the third week of the disease. Infective larvae may be found as ear as the seventeenth day of infection (Nolf and Edney, 1935). After a numl of months the cyst wall becomes thicker and may begin to calcify and droplets are sometimes found at the poles. Encysted larvae often rem viable and infective for many years even though the cyst walls may be cified. The encysted larva dies when it becomes calcified itself.

PATHOLOGY AND SYMPTOMATOLOGY

From a consideration of the life cycle of *T. spiralis* one can under why the pathology and symptoms of the disease are very numerous and unpredictable. The degree of parasitism is probably the most important in determining the severity of the disease in individual cases. In other the symptomatology, pathology, and prognosis depend to a large exten the number of infective larvae ingested, the life span of the adult f the number of young larvae deposited and the organs invaded by these.

The question concerning the dose of larvae lethal for an animal cult to answer. Rappaport (1943a) found that it was almost impossibl dict the survival time of mice unless massive doses of larvae were gi receiving over 90 larvae per gram of body weight in most instances tween the third and fifth days of infection. McCoy (1932) with found that a dose of 5 larvae or more per gram of body weight was fatal in 3 to 41 days. Craig and Faust (1945) estimated the letha man to be about 5 larvae per gram of body weight.

perivascular tissues The finding of migrating larvae *in the areas of cellular infiltration may* be the only pathologic finding in the section whereby one can differentiate between trichinous and other encephalitides Similar lesions may be seen in the spinal cord The spinal fluid is usually clear under pressure *and may contain young larvae*

Other organs such as **liver, kidney, spleen pancreas** and **bone marrow** are infrequently involved to any serious degree Fatty changes may occur in the liver and kidneys The lymph nodes may be mildly inflamed larvae in such instances are occasionally found in the marginal sinuses (Fig 203) The bone marrow may be hyperplastic and show a preponderance of eosinophilic myelocytes Larvae breaking out of the capillaries may cause subcutaneous petechial and subungual hemorrhages accompanied by a pruritis Capillary hemorrhage of the eyelids and conjunctiva occurs commonly and may be one of the causes of the prominent facial edema as discussed below Bulbar chemosis is a frequent manifestation Fever is an important and prominent symptom but this may be a direct result of the muscle involvement

Musculocystic Phase

The most seriously involved organs of the body during the migratory stage are usually the muscles in which most of the larvae finally encyst Some authors prefer to include the pre encystment muscular phase with the migratory phase of the disease Since however the entrance of a young larva into a muscle fiber is a definite entity and is really the beginning of the final encystment stage it is felt that the invasion of the musculature should be considered separately Furthermore exclusion of the voluntary muscle involvement from a discussion of the migratory phase emphasizes the importance of larval migration into other organs a matter which is so often overlooked *in general descriptions of the disease* The average medical student and practitioner usually have only a vague idea of the life cycle of *Trichinella spiralis* and think only in terms of adult worms in the intestine and coiled encysted larvae in voluntary striated muscles

In heavy infections practically all voluntary muscles are affected There seems however to be a greater invasion of certain muscle groups especially those of the diaphragm tongue shoulders neck thighs cheeks and eyes Why these muscles are more favored for encystment is not definitely known Lewis (1928) believed that muscle glycogen plays an important role that those muscles low in glycogen content are most frequently affected Such muscles are usually the most active possess a greater blood supply and probably therefore are exposed to greater parasitization Attempts however to produce paralysis or to increase the blood supply of certain muscles did not result in any appreciable difference in the extent of invasion by larvae (Berger and Stahelin 1928 Scheifley 1937)

The young migrating larvae break their way out of the muscle capillaries and enter the adjoining connective tissue (Hertwig and Graham 1895 Gra

with the greatest migrations of larvae occurring between the second and fourth weeks of the disease. Owing to the varied symptoms differential diagnosis is very difficult.

In the lungs the larvae may produce catarrhal and embolic phenomena with marked congestion and edema. Small petechial hemorrhages are often noticed. Hemoptysis is an occasional symptom. Bronchopneumonia is a complication to look for; it may occur as early as the fifteenth day but more often during the fourth to sixth week of the disease.

Trichinous myocarditis is an important and common manifestation. Many workers believe that this condition results from a toxemia since larvae are infrequently found in heart muscle. The reason for this is probably that by the time a patient comes to autopsy the larvae have migrated out of the heart muscle and into the pericardial cavity. Figs 254 and 255 illustrate the early stages of cardiac muscle degeneration; both are a little too early to show the extensive cellular infiltration rich in eosinophiles which occurs during the third week of the disease. Electrocardiographic findings in lighter infections may demonstrate temporary flattening of the T waves, low amplitude QRS, left axis deviation, nodal premature contractions, prolongation of PR interval, and other changes. In more severe cases there may be an intraventricular block resulting from injury to the conducting mechanism (Spink 1935, Cushing 1936, Beecher and Amidon 1938).

A case of trichinosis of the myocardium was reported by Terry and Work (1940). This case was misdiagnosed as acute rheumatic fever and not until autopsy was the true cause determined when *T spiralis* larvae were found in the heart muscle. The heart was dilated with a few small hemorrhages in the subepicardial fat. The myocardium was pale reddish brown, dull and flabby, with no fibrosis or mural hemorrhages. Microscopically the larvae were found between swollen hyalinized muscle fibers surrounded by collars of eosinophiles, lymphocytes, neutrophiles, histiocytes and a few plasma cells.

T spiralis larvae never encyst in heart muscle. They are usually found between the cardiac muscle fibers and sometimes within a fiber. The reason that they do not complete their development in the heart has never been answered adequately. It is probable that the rapid movement of this organ forces the larvae out of the cardiac fibers which possess a sarcolemma much finer and less firm than is found in voluntary striated muscle (Askanazy 1895, Graham 1897, Hemmert Halswick and Bugge 1934).

The central nervous system is another important region which may be affected during the migratory phase. Nervous disorders are often encountered which may vary from headaches to convulsions, hemiplegia, encephalitis and meningitis, with changes in various neurologic signs and reflexes. The gross pathologic findings vary with the symptoms. Frequently there are scattered punctate hemorrhages; in some cases with intense meningeal congestion, edema and vacuolization of the cortex. Microscopically the pathology is often indistinguishable from that of epidemic encephalitis,* with characteristic cuffing of the

*Syverton et al (1947) were able to transmit the virus of lymphocytic choriomeningitis by means of *T spiralis* infections.

bacteriemia may be another cause of fever but such a complication is rare A low grade fever may begin during the early part of the intestinal phas and increase in intensity as the muscles become affected In other instances the fever might not make its appearance until the second or third week of the infection

Facial edema is frequently the earliest important symptom to be noticed and may occur as early as the seventh day, although its onset is usually during the second or third week of the infection It persists about a week and in some instances may recur It begins as a circumorbital swelling which is so

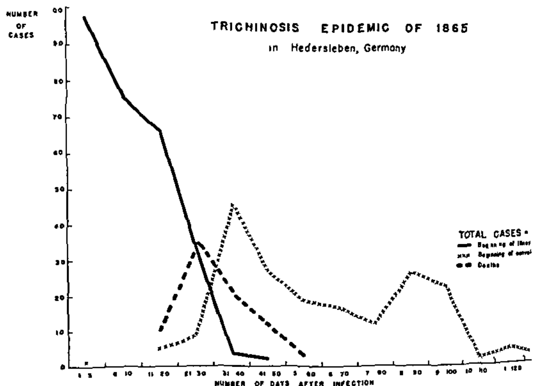


Fig 261 —Graph illustrating the course of the 1865 trichinosis epidemic in Hedersleben Germany The total population of the city was 2 000 337 became ill of which 101 died. Of 280 cases included in this graph there were 84 deaths 64 of which were due to respiratory paralysis the single death occurring after 195 days was associated with an old tuberculosis (From data compiled by Kratz 1866)

inflammatory in nature as to simulate a pansinusitis (Pepper, 1931) Ophthalmologic services are frequently the first to be visited by the patients The cause of this facial edema is not known It is believed to be the result of both the direct migration of young larvae into the subcutaneous tissues and conjunctiva, and parasitization of the superficial facial muscles A dependent edema may occur later but this may be the result of myocarditis

The muscle tenderness, pain, and edema are usually in the large muscle masses such as the thighs, calves, shoulders, and back Mastication and deglu

ham 1897) From there they make their way into muscle fibers The earliest changes of a parasitized fiber are seen in the striations which are bent forward by the larva The fiber protoplasm then begins to take on a granular appearance staining basophilically Within a short time the nuclei of the fiber become enlarged (Fig 257) and may be so conspicuous that in some instances they may be as large as half the diameter of the fiber The larva within the fiber apparently feeds on the muscle protoplasm and glycogen As a result of disintegration products and movements of the larva the fiber swells considerably (Figs 256 and 257) During the early development of the larva in the fiber there is often very little cellular reaction except at the poles of the region parasitized The sarcolemma takes on a thick gelatinous appearance which ultimately forms the cyst wall The poles of the cyst are closed off later apparently by the action of the numerous cells in those regions Graham (1897) was of the opinion that the sarcolemma plays an important role in the protection of the cyst from infiltrating leucocytes and that if these cells do succeed in penetrating the sarcolemma the larva will be destroyed (Fig 259) The cellular reaction around the cysts becomes more prominent (Fig 258) and later a fatty infiltration may be noted at the poles The cyst wall continues to grow in thickness and after a number of months the cellular and fatty reactions diminish in intensity (Fig 260) Just within the cyst wall and about the larva may be seen remnants of the muscle fiber and its nuclei (Figs 258 and 260) occasionally there may be more than one larva within a cyst Calcification of the cyst wall occurs slowly and may after a number of years become complete

Muscle fibers adjacent to those parasitized are also affected This is probably the result of a local toxemia or pressure on them by the swollen parasitized fibers These adjacent fibers show evidence of degeneration as exemplified by fragmentation hyalinization and granulation Their nuclei may also become considerably enlarged A cellular infiltration may sometimes be found within nonparasitized fibers

The symptomatology during the early musculocystic stage may be complicated by the involvement of organs other than the muscles The most prominent symptoms are however those arising from the invasion of the muscle fibers themselves

Fever almost always accompanies the early phase of muscle invasion It is usually of a remittent type and may vary from 101° to 105° F the intensity often depending upon the severity of the infection Only occasionally may there be a chill The duration of the fever may be from several days to a month or more and is likewise related to the severity of the parasitism The cause of the increased temperature is not definitely known but it may be the result of extensive degeneration of tissues and larvae during their migrations and development in the musculature The increase in muscle lactic acid creatine and purine bases during the disease are further indications of extensive degenerative changes in the musculature (Flury 1913 Flury and Groll 1913 Herrick 1915 Harwood Spindler et al 1937) A secondary

DIAGNOSIS

The diagnosis of trichinosis is often very difficult. A large percentage of cases, even severe ones, are frequently misdiagnosed. Diagnosis is made by history and clinical findings, immunologic tests, and demonstration of the parasite. The last named method is by far the most reliable.

History and Clinical Diagnosis

Perhaps the most common findings in a case of trichinosis are fever, facial *edema, myositis, and a high eosinophilia not associated with any allergy or* other parasitism. It may be well to summarize the symptomatology by listing various other diseases and conditions with which trichinosis may be confused (Hall 1937, Kaufman 1940, Gould 1945, and others).

Intestinal derangements	Infectious gastroenteritis Food poisoning Intestinal influenza Colitis Dysentery Cholera
Fever and headache	Grippe or influenza Septicemia Undulant fever Typhoid fever Fever of undetermined origin
Edema	Acute nephritis Sinusitis Dermatomyositis Mumps Angioneurotic edema Acute alcoholism
Neurologic	Poliomyelitis Encephalitis Meningitis Polyneuritis Periarteritis nodosa Cerebral thrombosis and hemiplegia Chorea Amyotrophic lateral sclerosis Psychoses
Cardiac	Rheumatic fever Endocarditis Myocarditis
Pulmonary	Pneumonia Hemoptysis Bronchitis Pleurisy Asthma
Skin	Scarlet fever Measles Rickettsial diseases Syphilis
Myositis	Grippe or influenza Tetanus Acute appendicitis or acute surgical abdomen Gall bladder disease Peptic ulcer Renal colic Beriberi Muscular hypertrophy *Botulism*

tition are painful Hoarseness is a symptom resulting from invasion of muscles and tissues of the larynx, glottis, and pharynx Respiratory difficulty is often encountered, as emphasized in Kratz's (1866) report of the Hedersleben epidemic in which 64 of 84 deaths were due to respiratory paralysis Muscle contracture, spasm, stiffness, and weakness are other frequent muscular symptoms These muscular conditions are the direct result of damage to the muscle fibers by the invading and encysting larvae They attain their peak in 4 to 6 weeks and may not subside completely for many months

CLINICAL LABORATORY FINDINGS

By far the most common finding in trichinosis is a leucocytosis of between 10,000 and 20,000, sometimes as high as 75,000 This leucocytosis is mainly due to an increase in the eosinophiles which in the differential count may be as high as 80 per cent The eosinophilia may occur as early as the seventh or eighth day but is often not evident until the third week of the disease It progresses rapidly to a peak but frequently exhibits considerable daily variations After the peak is reached in about the fourth or fifth week, there is a steady decline over a period of months and even years The peak is usually reached after the most severe symptoms of muscle invasion have passed Many workers do not feel that the extent of eosinophilia is an indication of the severity of the disease, but Brown (1897) believed that the eosinophilia varied directly with the muscle symptoms In severe, fatal cases, the eosinophile count may drop rapidly before death As for the differential count in severe, nonfatal cases, it is not unusual to find an eosinophilia above 50 per cent and the neutrophiles as low as 6 per cent, the latter varying inversely with the number of eosinophiles Lymphocytes are often reduced in the differential count but they usually show an increase with the subsidence of the eosinophilia Monocyte counts may show slight fluctuations Erythrocyte counts may be increased early in the disease as a result of dehydration, later, there may be a mild anemia which usually does not fall below 3 000,000 per cubic millimeter Other hematologic findings are relatively normal, except for an increase in eosinophilic myelocytes in examination of sternal bone marrow and, possibly, a prolongation in blood coagulation time

The urine is often normal, but albumin a trace of sugar, a few hyaline and granular casts, several erythrocytes and leucocytes and a positive diazo reaction may be present

Blood chemistry determinations usually do not offer much information concerning the disease The variations from the normal may be slight changes in blood sugar, calcium phosphorus ratio, cholesterol, bilirubin, and nonprotein nitrogen during the early part of the disease Hanes (1936) reported a case with severe edema, hypoproteinemia, and a reversal in albumin globulin ratio which were believed to have been the result of vomiting and starvation

The spinal fluid is usually normal, but in cases of encephalitis, it may be under pressure The cells, mainly lymphocytes, may be slightly increased in number Rarely is blood present

Identification of the Parasite

Examination for Adults—Only rarely are *T spiralis* adults found liquid stools Since this type of examination is so frequently unsuccessful it not encouraged

Examination for Migrating Larvae—Young larvae may be found in the blood and spinal fluid during the migratory phase especially in heavy infections These larvae are found during the second week of the disease and m be present until the fourth week or longer The most common method to hemolyze 1 to 5 c c of unclotted venous arterial or capillary blood in volumes of a dilute acid such as 3 per cent acetic acid After laking th material is centrifuged The entire sediment is then examined microscopical either as a fresh wet preparation under a cover glass or as a stained smea The larvae are easily recognized under low power magnification by their si (about 0 1 mm) In cases with hemoptysis young larvae may be seen in th sputum in central nervous system involvement they may be found in cen trifuged spinal fluid Migrating larvae might be found in other parts of th body such as in fluid obtained by duodenal intubation but such examinatio is not often successful

Larvae in the Musculature—Finding larvae in the musculature is by fa the surest method and is often positive in moderate and heavy infections I the pork consumed by the patient is still available examination of it shoul be made Larvae may be found in biopsies of the deltoid or other suitabl muscles quite early in the disease although they are usually not presen in appreciable numbers until the end of the second week There are sever methods of examining the musculature by pressed preparations sectioning and peptic digestion

The *pressed preparation* is the simplest and most useful method A fe small particles of muscle are placed between two 2 by 3 inch glass slides an the slides are bound tightly together with rubber bands The entire biops material is then examined under a dissecting microscope or under the low power objective of a compound microscope Immature as well as matur encysted larvae are readily seen by this method

Histologic sectioning and staining of the biopsy specimen is frequentl used offers permanent preparations and enables one to study the pathologi changes in the muscle It has its disadvantages however in that the entir biopsy specimen is not examined unless serial sections are made

Peptic digestion involves mincing and treatment of the specimen at 37° C with shaking in 30 volumes of 0 5 per cent hydrochloric acid and 1 per cen pepsin until it is completely digested The entire material is then strainec through a 40 mesh sieve sedimented and washed in water by resedimentation when the supernatant fluid becomes relatively clean the sediment is examinec microscopically (Fig 248) This method is useful only when the larvae in the musculature are mature since immature larvae are not resistant to digestion Mazzotti and Pastrana (1943) found the compression method superior for examination of diaphragms

Grippe and influenza acute nephritis sinusitis typhoid fever and rheumatic fever are the commonest diseases with which trichinosis is confused

Immunologic Tests

Immunologic tests are excellent means of aiding in the diagnosis and are considered highly presumptive or even specific by some workers The two most popular are the intradermal and precipitin tests There have been numerous papers published on the preparation of antigen for these tests Probably the best and simplest method is that of Bozicevich (1938) using a saline extract of dried, powdered *T spiralis* larvae obtained by pepsin hydrochloric acid digestion of the musculature of heavily infected rats The extract is prepared in a stock solution of 1 20 of the dried powder and sterilized by heat at 58° C Precipitin ring tests are made with dilutions of 1 100 to 1 5 000 or higher Nonspecific reactions may occur in dilutions up to 1 500 and it is therefore best to determine the highest titer which will give a positive reaction

The intradermal test is made with 0 01 c c of dilutions of 1 10 000 1 8 000 and even 1 5 000 There are 2 types of reaction in the intradermal tests immediate and delayed In the immediate type a blanched wheal of 5 mm or larger with or without pseudopodia is formed within a period of 10 to 30 minutes In most instances the reaction is considered positive if the wheal formed by the extract exceeds that of the control (saline in the case of Bozicevich s antigen) by 3 mm or more In the delayed reaction occurring in a small percentage of cases there is a reddish edematous area about 2 or 3 mm in diameter which forms and diminishes slowly with its peak at about 12 to 24 hours

The intradermal test is more sensitive becomes positive earlier and lasts longer than the precipitin test The latter becomes positive usually during the fourth week of the infection and persists for a varying length of time sometimes as long as 1 to 3 years The intradermal test becomes positive usually during the third week of the infection and may persist for as long as 7 years or longer The delayed intradermal reaction is more frequently found during the early stage of the infection Both tests together are excellent for diagnosis If a positive skin test and a negative precipitin test are encountered throughout the illness it is possible that the patient may have had a previous infection and does not have acute trichinosis If the skin test is positive and the precipitin test changes from negative to positive during the course of the illness the indications are strongly in favor of the view that the patient is suffering from the acute stage of trichinosis

A small percentage of individuals however exhibit false positive reactions the reasons for which are not known False positive reactions have been reported in other worm infections (Augustine 1937), periarteritis nodosa infectious mononucleosis (Bassex Thomson and Silver 1949) and neoplastic diseases of the reticuloendothelial system (Southam Thomson and Burchenal 1949) Frequently the complement fixation and skin tests will be negative while the precipitin test may be falsely positive

An important consideration is the diet of the patient Hanes (1936) reported a case exhibiting severe edema and hypoproteinemia resulting from starvation In experiments with mice (Rappaport, 1943a) it was found that animals receiving a mash of bread and milk survived larger doses of *T spiralis* larvae than those kept on a diet of solid food and water In many instances mice were found dead with their mouths filled with soft food and their stomachs empty apparently because deglutition was exceedingly painful Heavily infected animals frequently died during the second and third weeks of infection if they were deprived of soft food for as short a period as 5 hours

Very little experimental work has been done in regard to diets in the control of the acute stage of the disease Vitamin A deficiency may cause a persistence of female worms in the intestine and thus result in a larger number of larvae deposited by them (McCoy 1934) Excessive vitamin loss is an important factor in any febrile condition Vitamin therapy with proper diet is therefore probably essential in the management of the acute stages of trichinosis

The above symptomatic and dietary treatment should be continued as long as indicated Complete bed rest is by far the most important and should be continued until the myocarditis and acute myositis subside sufficiently During convalescence muscular exertion and fatigue are not desirable

PROGNOSIS

The prognosis is dependent upon the initial dose of larvae ingested and other factors which may influence the course of the disease such as immunity from a previous infection resistance of the patient and organs involved during the migratory phase Some workers feel that an early mild or moderate diarrhea is a favorable sign since developing larvae and adults may be more easily eliminated Severe dysenteric symptoms are often a poor prognostic sign Likewise symptoms of myocarditis encephalitis pneumonia and later respiratory paralysis indicate a questionable prognosis A sudden fall to normal of the eosinophile count and a sudden change in the immunologic tests from positive to negative are often bad omens

The course of an epidemic in regard to the beginning of illness (incubation period) deaths and the beginning of convalescence is illustrated in Fig 261 In most instances the incubation period is early Deaths occur during the second to sixth week Convalescence is a long drawn out process which may last for many months as indicated by early fatigue and muscular weakness Excessive damage to the heart and central nervous system may be permanent In regard to the influence of *T spiralis* on tumor formation there is no authentic evidence of such complication resulting directly from the parasitism

PREVALENCE

Trichinosis is found in most parts of the world especially in regions where garbage feeding of hogs is a common practice and pork is consumed in a raw or partially cooked state Autochthonous cases have not been reported from

X-ray may be used for diagnosis of very old cases of trichinosis since calcified cysts are seen on a properly exposed x-ray plate. This method however is rarely used except academically or for diagnosis of persistent "rheumatic" pains and weakness of the musculature.

IMMUNITY

There is little information published in the literature concerning immunity to trichinosis in human beings. It is believed that it may play a role in reducing the extent of recent infection if the individual had previously consumed very lightly infected undercooked pork on several occasions and had in this way acquired nonclinical trichinous infections. This view is held by many workers. Many authors, however, have reported the finding of young and old calcified cysts side by side in sections of muscle. Animals previously infected exhibit an early expulsion of larvae and adults from the intestine and an increased tolerance to massive doses of larvae (McCoy, 1931a, 1939, 1940; Bachman, 1938; Roth, 1939, 1943; Rappaport and Wells, 1949; and others). The question of immunity in human beings, therefore, remains unanswered at the present time. All one can say is that it may influence the infection to some degree but there is no absolute immunity produced.

TREATMENT

Some workers (Gould, 1945) feel that treatment with an antiserum may be beneficial. It is felt, however, that there is no satisfactory experimental evidence for its justification. Most work has been done with animals passively immunized with antiserum before and immediately after infection and not at a time when diagnosis is most apt to be made, e.g., during the second week.

There is no specific treatment for trichinosis. Some textbooks advise the use of cathartics and anthelminthics to eliminate the adults from the intestine, but there is no experimental justification for such procedure.

To date the only treatment of any value during the acute stages of the disease is symptomatic treatment. Complete bed rest is essential for the management of the fever, myocarditis, myositis and other symptoms. An attempt should be made to anticipate the symptoms and to treat each symptom as it develops. Thus, if there is dehydration due to excessive diarrhea, vomiting and perspiration, parenteral fluids are indicated. The diarrhea may be treated with bismuth and paregoric, constipation with mild salts. In the event of a myocarditis and heart failure, restriction of salt may be advisable. Conjunctivitis may be treated symptomatically. Central nervous system involvement may be relieved by lumbar taps. If shock develops, either intravenous plasma or blood transfusion is advisable. Pneumonia is a complication to be guarded against. Analgesics, sedatives and even morphine are often useful in relieving the myositis. Sponge baths with tepid water are helpful. A developing anemia is treated with iron. In the event of respiratory paralysis, the use of a mechanical respirator is indicated. In a similar manner the other numerous symptoms may be treated.

Inspection of freshly killed hogs for trichinosis is not a routine procedure in the United States since most hogs are so lightly infected that they may be missed Such inspection would, therefore, lead to a false sense of security The method of skin testing of hogs may prove useful but it is still in the experimental stage and would probably be a difficult procedure to carry out in most abattoirs

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Cuba (Kouri Basnuevo and Sotolongo 1943) Puerto Rico (Bachman Molina and Oliver Gonzalez 1934) and a number of other Latin American countries where it is a common practice to cook pork well In surveys of cadavers and by skin testing Perrin (1942) and Mazzotti and Hube (1944) found an incidence as high as 12 5 per cent in Mexico City Martinic (1942) found an incidence of 13 per cent in Santiago Chile Cases of trichinosis have been reported from Brazil and British Guiana (McKinley 1935)

Surveys of thousands of cadavers after autopsy indicate that the parasitism is less in the southern United States On the whole it is estimated that about 15 per cent of the entire population in the United States have been infected with *T spiralis* at one time or another (Hall and Collins 1937 Hall 1938 Sawitz 1939 Catron 1940 Kerr Jacobs and Cuvillier 1941 and others) Only about 2 5 per cent of those infected however had histories of clinical symptoms of the disease (Wright and Brady 1940) Trichinosis is therefore quite widespread but owing to the fact that most cases are usually very light they are missed or overlooked

Many cases of trichinosis are familial and local in origin Outbreaks frequently occur in isolated families or groups after a meal of inadequately processed or cooked pork from a locally slaughtered hog Many cases also result from eating hamburgers adulterated with pork scraps The sale of such beef hamburgers is forbidden by law in many places but nevertheless they are still sold at many small lunch counters Jerked bear meat has been reported as a cause of minor outbreaks among hunters and even dog meat has been known to cause outbreaks in man

The disease is usually transmitted from hog to hog by the feeding of uncooked garbage containing pork scraps In the United States surveys have shown that about 10 per cent of garbage fed hogs and only 1 per cent of grain fed hogs are infected with *T spiralis* (Wright and Brady 1940) Rats and mice probably play a role in maintaining the infection in nature

PREVENTION

Obviously the control of the disease is important and involves both the proper care and feeding of hogs on the part of the farmer and adequate processing of pork and pork products by meat packers and housewives If garbage is to be fed to hogs it should be thoroughly cooked Hogs should be raised on sanitary farms where the rodent population is kept at a minimum

Pork products (salted smoked etc) under United States Government inspection are safe without cooking It has been found that larvae may remain alive up to 300 days in pork kept at ordinary refrigeration temperature Pork however may be made safe for eating by refrigeration at 5° F for 20 days as is required by the United States Department of Agriculture Augustine (1933) reported that quick freezing at −34 6° C for about 6 hours results in the destruction of larvae The best advice to housewives is thorough cooking of pork for a period long enough for the center part of the meat to become thoroughly done

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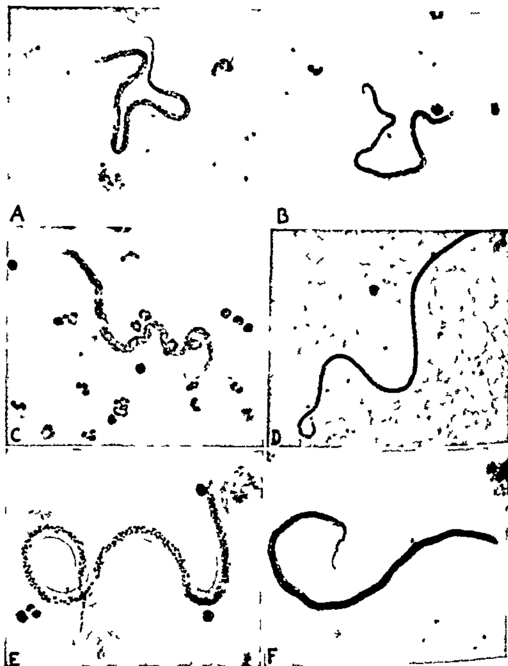


Fig 262—Microfilariae. Original photomicrographs. (×840) *A Mansonella ozzardi* and *B Acanthocheilonema perstans* from stained films received from Harry Schwachman. *C Wuchereria malayi* from Candido Africa. *D Acanthocheilonema streptocerca* from Louis van den Berghe. *E Wuchereria bancrofti* from F. W. O'Connor. *F Loa loa.*

CHAPTER 39

FILARIASIS

Donald L. Augustine

Filariasis is an infection with nematode parasites of the superfamily Filarioidea in which clinical manifestations may be either present or absent. *The parasites are commonly known as filarial worms.* *The adults or parental* forms of this group are long and thread like. They are characteristically tissue parasites inhabiting the lymphatics, blood vessels, connective tissues or serous cavities of land vertebrates, namely frogs, lizards, birds and mammals. The progeny of the adult worms are motile larvae and because of their minute size are known as microfilariae. These microfilariae are deposited with or without periodicity within the body of the host and must escape through the skin during the feeding of a bloodsucking insect for further development and transmission to a new host. Whereas adult filarial worms are markedly host specific, the ability of microfilariae to develop in a wide range of bloodsucking arthropods, particularly mosquitoes, is a prominent feature of the group. The parental forms of most species of filarial worms infecting man have been studied by relatively few workers. They rarely enter in the diagnosis and therefore only references to original studies on their morphology and taxonomy will be recorded here. Specific diagnosis is usually established on morphologic and biologic characters of microfilariae.

CAUSAL AGENTS

Of the great number of species of filarial worms only *Wuchereria bancrofti* (Cobbold 1877) Seurat 1921, *W. malayi* (Brug 1927) Rao and Maplestone 1940, *Onchocerca volvulus* (Leuckart 1893) Railliet and Henry 1910* and *Loa loa* (Cobbold 1864) Castellani and Chalmers 1913 are important pathogens for man. Less important species infecting man include *Mansonella ozzardi* (Manson 1897) Faust 1929, *Acanthocheilonema perstans* (Manson 1891) Railliet, Henry and Langeron 1912, *A. streptocerca* (Macfie and Corson 1922) and a number of forms known only in the microfilaria stage.

These later named species, while of questionable pathogenicity, must be *considered in establishing a specific diagnosis and knowledge of their geo*graphic distribution and characteristics of their microfilariae is therefore essential. They will be briefly discussed in the following paragraphs and will not receive further attention.

Mansonella Ozzardi (Manson 1897) Faust 1929

Mansonella ozzardi is limited geographically to Central America, the northern countries of South America, the northern states of Argentina and probably occurs in most of the

*Onchocerca volvulus and onchocerciasis are given detailed discussion in Chapter 40.

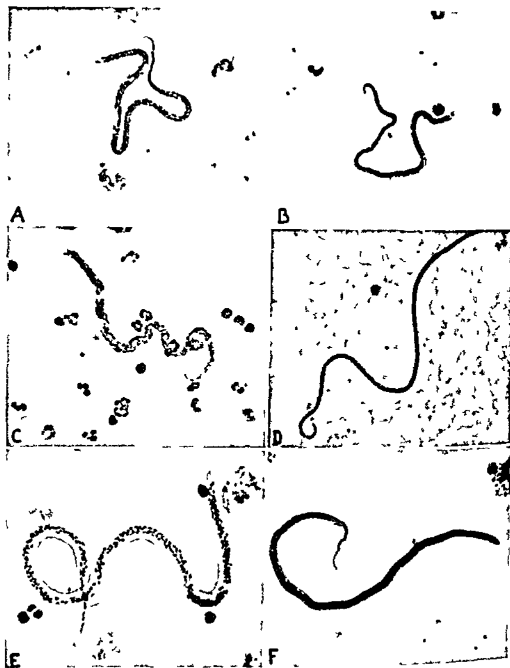


Fig 262—Microfilariae Original photomicrographs (×840) *A Mansonella ozzardi* and *B Acanthocheilonema perstans* from stained films received from Harry Schwachman *C Wuchereria malayi* from Candido Africa *D Acanthocheilonema streptocerca* from Louis van den Berghe *E Wuchereria bancrofti* from F W O'Connor *F, Loa loa*

islands of the West Indies Like all other filariases, the distribution is discontinuous and spotted within the endemic countries The incidence of infection is likewise variable, but in some native villages over 50 per cent of the inhabitants have been found positive upon blood examination Our knowledge of the adult worms is based largely on the original studies of Daniels (1902) of a few specimens obtained at autopsy on a native of St Lucia by Dr O Galgey Five specimens, all female, were found in the connective tissue of the mesentery They varied from 65 mm to 81 mm in length, and from 0 21 to 0 25 mm in breadth The microfilariae are very small, usually not more than 200 microns in length and 5 microns in breadth They show no periodicity in the peripheral blood, they are exceedingly active in fresh blood films, and in stained films they assume outlines of small bowknots They are unsheathed and have a sharply pointed tail, free of nuclei, a character which early suggested the common name, "the sharp tailed filaria of British Guiana" Development of the microfilaria is completed in the midge *Culicoides furens*, which insect is believed to be the usual vector (Buckley, 1934)

This organism apparently does not cause clinical symptoms

Acanthocheilonema Perstans (Manson, 1891) Railliet, Henry, and Langeron, 1912

Acanthocheilonema perstans except for its apparent absence in the Greater Antilles, has a geographic distribution in the Western Hemisphere similar to that of *Mansonella ozzardi* In some localities it has been known to be characteristically limited to coastal areas, whereas *M ozzardi* may extend inward along river valleys (McCoy, 1933) *A perstans* in the Americas is probably of African origin where its incidence is high throughout west coastal countries and the Congo Basin

The parental worms were first discovered by Daniels (1902) in British Guiana and were accurately described in 1903 by Low They occur in the connective tissue of the mesentery, perirenal and retroperitoneal tissues, the pericardium and occasionally in subcutaneous cysts The microfilariae were first discovered by Manson in 1891 in the blood of a West African Negro suffering from sleeping sickness in the London Hospital They are unsheathed, non periodic microfilariae They are practically identical in size with the microfilariae of *M ozzardi*, but can readily be identified in stained films by the bluntly rounded caudal extremity containing prominent nuclei to its tip (Fig 262) In Africa, the midge *Culicoides austeni* is a known vector of *A perstans* (Sharp, 1928) Its vector in the Americas has not been identified

A perstans is not believed to cause disease, except allergic phenomena

Acanthocheilonema Streptocerca (Macfie and Corson 1922) Stiles and Hassall 1926

Microfilariae of *Acanthocheilonema streptocerca* were first discovered in small pieces of skin of healthy natives of the Gold Coast, Africa, and later reported in natives in the Mamfe division of the British Cameroons About 50 per cent of the inhabitants in some villages have been found infected The microfilaria is unsheathed, and, in stained preparations, it averages 215 microns in length, its greatest diameter being about 3 microns It strikingly resembles a shepherd's staff with its crook at the caudal extremity (Fig 262) In stained sections of parasitized skin the microfilariae lie in the tissue spaces of the corium, usually close to the rete mucosum They do not occur in the blood. It is not unusual for native inhabitants to show simultaneous infection with *A streptocerca*, *O volvulus*, and *A perstans* Very recently, Peel and Chardome (1946) reported the finding of the parent worm (*female*) of *A streptocerca* in the chimpanzees *Pan paniscus* and *Pan satyrus* in the Belgian Congo

Wuchereria Bancrofti (Cobbold, 1877) Seurat, 1921

BANCROFTIAN FILARIASIS

HISTORICAL

The enormous enlargements of parts of the body, particularly of the legs and external genitals, so frequently accompanying bancroftian filariasis, were noted and much studied long before the etiologic agent, *Wuchereria bancrofti*, was discovered According to Menon (1935) the first, and a very good description, of these conditions was written about 600 B C by Sushruta in India The disease was probably also known at that time in Persia, Arabia, Egypt, and parts of Africa Hillary (1766) gives a very good account of its occurrence in Barbados, describing the recurring attacks of fever, the lymphangitis, the lymphadenitis, and the slowly increasing swellings of the affected part up to the stage at which typical elephantoid appearances become definite and prominent Hillary was certain that the disease had been brought to the West Indies from Africa by Negro slaves and, at his time, was observed to be "too frequent among them and among the white people also" Neumann (O Connor and Beatty, 1938) estimated that, in 1881, 6 per cent of the population of St Croix, Virgin Islands, had elephantiasis

Observations demonstrating the etiology of elephantiasis were initiated in 1863 by the French surgeon, Demarquay, who found microfilariae in chylous urine of a person who had lived in Cuba, were continued by Lewis (1879) in India, and culminated in the research of Patrick Manson in China between 1876 and 1900 (Manson, 1903) Early in his investigations Manson discovered filarial periodicity and experimentally demonstrated that the mosquito *Culex quinquefasciatus* was an essential intermediate host and the common agent for dissemination of the parasite

In 1876 Bancroft in Australia discovered an adult female specimen in a lymphatic abscess This was described as *Filaria bancrofti*, Cobbold, 1877 Twenty five years ago it was removed from the genus Filaria and placed under the genus Wuchereria, a name which had been applied to it in 1877 by da Silva Araujo of Brazil in honor of Dr Wucherer, a prominent Brazilian physician and parasitologist of that time Later investigations were largely directed along epidemiologic and pathologic lines Noteworthy among these are the studies by Bahr (1912), O'Connor (1923, 1932), Anderson (1924), Fulleborn (1929), Iyengar (1938), and Poynton and Hodgkin (1938) Keen interest in bancroftian filariasis developed during World War II following the report of its high frequency and its serious disabling effect in thousands of United States Navy personnel who were serving in the South Pacific areas

GEOGRAPHIC DISTRIBUTION

Wuchereria bancrofti is widespread in tropical and subtropical countries It characteristically occurs in island populations or along more or less broad, low lying coastal areas of the larger islands and continents Indigenous infections are seldom to be found in the foothills or beyond coastal plains

In Asia, the parasite is established along the coastal areas from Arabia to the Shantung province in Eastern China It is prevalent throughout the islands of the East China Sea, southern Japan, southern Korea, and the Oceanic Islands In Australia its distribution is mainly limited to the Queensland coasts In Africa the infection is found in a few east and west coastal areas, lower Egypt, Madagascar, and neighboring islands Contrary to apparently current belief, it does not extend across tropical Africa, i e, it does not occur in the Central Congo areas (Rodhain, 1938, Brutsaert, 1944, van den Berghe, 1946) Brumpt (1936) does not include the Congo as an endemic area of bancroftian filariasis, and, according to Sharp (1928), the infection is rare or absent in the Mamfe area of the British Cameroons In the Americas, *W bancrofti* is very common along the northern coast of South America, particularly the littoral of the Guianas and Venezuela, to a lesser extent along the northern coast of Colombia, and it is generally prevalent throughout the Antilles

islands of the West Indies. Like all other filariases the distribution is discontinuous and spotted within the endemic countries. The incidence of infection is likewise variable but in some native villages over 50 per cent of the inhabitants have been found positive upon blood examination. Our knowledge of the adult worms is based largely on the original studies of Daniels (1902) of a few specimens obtained at autopsy on a native of St Lucia by Dr O Galgey. Five specimens all female were found in the connective tissue of the mesentery. They varied from 65 mm to 81 mm in length and from 0.21 to 0.25 mm in breadth. The microfilariae are very small usually not more than 200 microns in length and 5 microns in breadth. They show no periodicity in the peripheral blood; they are exceedingly active in fresh blood films and in stained films they assume outlines of small bowknots. They are unsheathed and have a sharply pointed tail free of nuclei, a character which early suggested the common name "the sharp-tailed filaria of British Guiana." Development of the microfilaria is completed in the midge *Culicoides furens*, which insect is believed to be the usual vector (Buckley 1934).

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seldom apparent and its existence is questioned (O'Connor, 1936). The body of the microfilaria is mainly composed of small nuclei A clear space, the nerve ring, is present at a point about ⅕ of the length of the body backward from the anterior end Another break in continuity of the nuclei occurs at about the junction of the upper ⅓ and the lower ⅔ of the body This second clear area is known as the "anterior V spot," or excretory pore. A smaller spot is visible a short distance from the end of the tail which is known as the "posterior V-spot" which represents the anal opening. The nuclei do not extend into the tip of the head or into the tip of the tail

KEY TO MICROFILARIAE OF MAN*

1 Microfilariae characteristically present in blood 2
Microfilariae characteristically present in lymph spaces of skin, no periodicity 9
2 Sheath present, periodicity 3
Sheath absent, no periodicity 7
3 Nocturnal periodicity (usually) 4
Diurnal periodicity 6
4 Tail tapering to fine point, nuclei do not extend to tip of tail, body assumes graceful, sweeping curves in stained film; length 300 μ ± .... *Wuchereria bancrofti* 5
5 Tail tapering to fine point but swollen at levels of 2 nuclei, body assumes stiff, irregular outline with sharp flexures in stained film; length 230 μ ± .... *Wuchereria malayi*
6 Tail tapering to fine point, nuclei extend to tip of tail, body assumes stiff, irregular outline with angular flexures in stained film; length 300 μ ± .... *Loa loa*
7 Tail sharply pointed, nuclei do not extend to tip of tail; length 200 μ ± .... [illegible] 8
8. [illegible]
9 [illegible] 10
10. [illegible]
curved, length 200 μ ± .... *Acanthocheilonema* [illegible]

In most endemic areas the microfilariae characteristically exhibit a marked nocturnal periodicity They are found in greatest number between 10 o'clock in the evening and 2 o'clock in the morning, but during the day usually few if any microfilariae are readily demonstrable in the peripheral blood We have no adequate explanation for this remarkable phenomenon In most areas of the Philippine Islands, however, and on some of the South Pacific Islands, namely, Tahiti, the Tonga, Fiji, Samoan, Wallis, and Ellice Islands, the microfilariae show no periodicity and remain in about equal numbers at all hours of night and day

For further development and dissemination of the parasite, the circulating microfilariae must be ingested by suitable mosquitoes, the sole vectors of bancroftian filariasis The factors which determine the suitability of particular mosquitoes are not known Development takes place readily in mosquitoes of a variety of genera, including *Culex*, *Aëdes*, and *Anopheles*, but closely related species within these genera differ widely in their ability to serve as hosts. For example, *Aëdes scutellaris pseudoscutellaris* is a very favorable host, but *A aegypti* and *A vexans* are not

Metamorphosis of the microfilariae and their development into the infective stage for man occur in the thoracic muscles of mosquitoes Under highly favorable conditions the infective stage is reached after about 10 days It travels through the thoracic muscles into the interior of the labium (the sheath which encloses the biting mouth parts), where it awaits an opportunity to get back to man, which opportunity is presented when the mosquito again feeds upon man Unlike the development of the malaria organisms in the mosquito, there is no multiplication of filaria larvae within the body of its vector. On the contrary, only a fraction of the number of the microfilariae ingested by the mosquito develop to the infective stage It has been estimated that about 35 per cent of the microfilariae ingested by mosquitoes die in the stomach blood clot, and that a very heavy mortality of larvae may also occur after

*Personal history of patient including travel likely exposure to filariasis and knowledge of the geographic distribution of filariid species should always be considered before diagnosis is established

The spread of bancroftian filariasis necessarily depends on the extent of the migration of individuals showing microfilariae in the blood on the presence or absence of appropriate mosquitoes in new areas to serve as intermediate hosts, on sanitation levels, and on favorable local meteorologic conditions

Although bancroftian filariasis is widespread throughout warm countries, it is always a focal infection, and is neither evenly distributed nor uniformly prevalent in any country The spotted and discontinuous distribution of the parasite within endemic areas is due to differences in local physical factors and sanitation, and to the presence or absence of favorable mosquito vectors A favorable high temperature with a suitable amount of moisture is absolutely necessary for the development of the parasite in the mosquito and for its transfer from the mosquito to human skin The low incidence of infection or absence of infection in many places, particularly in the interior of China where proved mosquito carriers are present, is attributed to cold or to dryness with high temperature (Feng, 1931) It is particularly difficult to understand why indigenous infections are rare if not absent along the Caribbean shores of Central and North America where conditions outwardly appear to be identical with those of the endemic areas of northern South America

Within endemic areas bancroftian filariasis primarily occurs in urban populations It is often restricted to a few towns or to sections of towns which are densely populated and where sanitary conditions are poor It is particularly common in overcrowded dwellings of poor people, and the incidence and morbidity in a given family may be striking

BIONOMICS

The parental forms of W *bancrofti* are parasites of the lymphatic system of man only They may be found at any point in the lymphatic system, but they occur most frequently in the limbs scrotum and inguinal regions The two sexes are frequently coiled together in the periglandular tissues the afferent lymphatics and in the cortical sinuses In heavy infections they may also occur in the medullary sinuses They probably do not migrate from the site of their development

The adult worms, like other nematodes show marked sexual dimorphism The male worm measures about 40 mm in length and 0 1 mm in diameter, and the female is at least twice as large Further anatomical details of the parental forms will not be recorded here since the adult worms seldom enter in the diagnosis When their identification is desired, the specimens should be examined by a person well experienced in nematode morphology and taxonomy

The microfilariae occur in the lymph the blood stream, and under certain conditions (chyluria) may be found in the urine In fresh preparations under low power of the microscope they appear as exceedingly active threadlike objects as they lash their way among the blood corpuscles Unless the slide is properly prepared and stained very little definite structure can be determined After staining with hematoxylin a certain amount of structure can be made out (Fig 265) They vary from 230 to 300 microns in length, and from 7 to 10 microns in breadth They are covered with a hyaline sheath which may extend some distance beyond the anterior and posterior limits of the body These sheaths are not apparent on the microfilariae in the circulating blood The sheath is formed on the slide in the clotting and drying blood The larva is mechanically held in the thickening medium, and in its efforts to push on and back out its outer covering is stretched It usually does *not escape* and the covering is retained as a distinct outer membrane (Augustine 1937) Bancroftian microfilariae are thus sheathed larvae and the presence of the sheath is a diagnostic character

In stained blood films the microfilariae assume a smooth graceful curve The head is rounded and it has been described as bearing a minute spear or stylet *This structure is*

study of intradermal and serologic tests for filariasis noted in some of their cases of bancroftian filariasis that an exacerbation of symptoms of lymphangitis together with pain in the scrotum and lymph glands followed the injection of small amounts of *Dirofilaria immitis* antigen

Early in the study of bancroftian filariasis it was believed that in addition to the presence of the worm itself traumatism or some other cause was needed to provoke lymph stasis and lymphangitis The British Filariasis Commission in 1924 went so far as to say that the worm per se produces no symptoms and that all the pathologic manifestations associated with filariasis are due to secondary infections by pyogenic bacteria To French scientists Montestruc and Bertrand (1937) and Chabeuf (1938) the parasite plays a more or less accidental role in the production of tropical lymphangitis or lymphatic filariasis and Grace (1943) holds that tropical lymphangitis is produced by a combination of lymph stasis caused by the parasite and subsequent infection by beta hemolytic streptococcus Dickson et al (1943) Michael (1944) King (1944) and Zuckermann and Hibbard (1945) having studied filariasis cases among United States Navy personnel who served in the South Pacific areas urged a return to the orthodox opinion of the direct responsibility of the worm for the clinical manifestations of bancroftian filariasis but the evidence on which bacterial infection was ruled out is not convincing The observations of Dubruel (1909) in Tahiti and neighboring islands are of interest Dubruel observed that fluid withdrawn in the presence of lymphangitis showed streptococci more frequently than that withdrawn between attacks This observation is in accord with the results of the experimental studies on elephantiasis by Drinker et al (1934, 1935) in which bacteria (streptococci) could rarely be isolated from edema fluid except at the beginning of an attack of chills and fever At the present time however most authors lean toward the view that the maturing and adult parasites and their secretions are responsible for the inflammatory reactions of bancroftian filariasis particularly in the early stages Some of the more serious later complications are obviously due to secondary infection

In most cases of bancroftian filariasis the living worms cause little or no damage other than varying degrees of blockage of afferent vessels of the lymph node (O Connor 1932, Hartz 1944) Their presence early causes simple dilatations of the vessel Occlusion of the vessel may follow due to an accumulation of epithelioid cells and lymphocytes within the lumen and its subsequent narrowing and obliteration by granulomatous perilymphangitis Severe inflammatory reaction giant cell formation and massive fibrosis are prominent in the environment of dead and dying worms the reaction becoming more marked with advancing disintegration and calcification of the parasites In heavy and long standing infections extensive areas can be involved resulting in complete obstruction of lymph drainage to a part development of lymphedema, and elephantiasis due to subsequent extensive fibrous overgrowth This sequence of events has been produced under ex

their arrival in the thoracic muscles (O Connor and Beatty 1938) The worms are pathogenic in the mosquito Many infected mosquitoes die during the first few days after an infective blood meal At every step of transmission, only a few parasites are involved The transmission of bancroftian filariasis is, therefore, accomplished with much less certainty than that of malaria.

When the mosquito feeds upon a person the infective larvae escape from the distal portion of the labium of the mosquito and momentarily become free on the skin They then actively enter the human host by penetrating the moist skin entering presumably through the wound made by the mosquito or through a breach in the skin

Nothing is known about the larvae after they enter the human host until they appear as adult worms in the lymphatic system Judging from observations on a related species *Dirofilaria immitis* found in the dog the development of *W bancrofti* to functional sexual maturity probably requires at least several months For production of microfilariae it is necessary that the worms of opposite sex come to lodge and develop together in the same spot Successful infections therefore probably are in most cases the result of mass biting by infected mosquitoes

PATHOLOGY

It must be admitted that great gaps still remain in our knowledge of the mechanics of pathologic changes in bancroftian filariasis Despite positive statements in the literature concerning the host parasite relationships these reactions remain largely an assemblage of ideas and lack experimental proof Experimental proof however is difficult because man is the only vertebrate host of *W bancrofti* and with the exception of the recent studies by Menon et al (1944) on lizard filariasis in India no similar histologic changes have been associated with any known filarial species infecting the lower animals

The disorders in bancroftian filariasis are usually attributed to interference with the lymphatic system It is generally held that living microfilariae are not particularly pathogenic Experiments have shown that living microfilariae readily pass unharmed through normal lymph nodes Direct observations have shown that they are exceedingly active in the blood stream They are not only carried about with the blood stream but they also actively move against the blood stream in the arterioles making slow progress by bracing themselves against the walls of the vessel They frequently occlude the capillaries and then suddenly break through the stagnated column of blood cells to re enter the active circulation They apparently never make permanent plugs or form emboli (Augustine Field and Drinker 1936)

In view of the fact that some probably many of the infective larvae which may gain entrance into the host may be destroyed before reaching maturity and that hundreds of thousands of microfilariae are constantly being destroyed within the body it is entirely possible that at least some of the manifestations of bancroftian filariasis are allergic responses The observation of Bozicevich and Hutter (1944) support this view These authors in a

Fig 264 —Sections of a degenerating adult *Wuchereria bancrofti* in the cortical sinus inguinal lymph node The vessel is completely obliterated following extensive fibrotic es (Original photomicrograph of material received from F W O Connor)

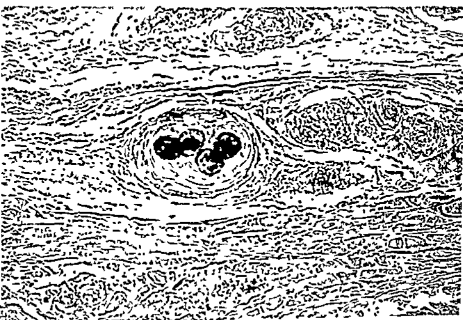


Fig 265 —Four sections of a calcified adult *Wuchereria bancrofti* in a subcutaneous vessel A focal spot Inflammation has subsided the vessel is occluded Note the tion of concentric rings of fibrous tissue (Original photomicrograph of material re- from F W. O Connor)

perimental conditions by Drinker and Homans (1934), who also demonstrated that loss of lymph circulation predisposes to bacterial (streptococcic) infection

Eosinophilic leucocytes may be rare or absent about living worms but characteristically occur in enormous numbers in the vicinity of dead and disintegrating parasites In the early stages of disease neutrophilic leucocytes may be absent from the cell picture thus indicating that the inflammation at this time is not necessarily caused by bacterial infection

The skin of elephantoid tissue in bancroftian filariasis is characteristically dense and leathery and because of destruction of the sweat glands is dry It may be smooth and glossy but it is frequently rough warty and even nodular Folds appear and deep abscesses frequently develop following abrasion and bacterial or mycotic infection



Fig 61 — Living female Wuchereria bancrofti in dilated lymphatic vessel near the testis There is no inflammation obstruction or hypertrophy of the vessel Note presence of myriads of ova and microfilariae in sections of the worm (Original photomicrograph of material received from Dr W O'Connor)

In the absence of demonstrable parasitism the pathology in bancroftian filariasis is essentially the same pathology as in sporadic cases of lymphadenopathy and elephantiasis in which filariasis is not a factor Elephantiasis grossly identical with bancroftian filariasis is common among natives of inland tropical Africa areas where *W bancrofti* is not indigenous To what extent this type of endemic elephantiasis resembles endemic bancroftian elephantiasis is not known (Sharp 1928 Rodhain 1938, Fruitsaert 1944 van den Berghe 1946)

curs in bancroftian filariasis When *not complicated by infection* the hydro cele fluid is clear and straw colored and *may contain microfilariae* Lymph varices frequently develop spontaneously without local or *general symptoms* and may become marked without the patients' *being conscious of them* Chyluria frequently develops upon rupture and drainage of a lymph varix into bladder *or kidney pelvis* *Here again* the onset is usually *abrupt often with* out warning but frequently preceded by pain or aching in the kidney *region* The urine may be chylous at one time but clear at another, *depending on* temporary closure of the ruptured lymphatic



Fig 206 —Elephantiasis of the legs attributed to bancroftian filariasis Three cases seen in British Guinea (Photograph by T H Weller)

Elephantiasis is the most striking phase of bancroftian filariasis The scrotum and legs are more frequently involved and less frequently the arms penis breasts and vulva Elephantiasis usually develops after repeated at tacks of lymphangitis The process may be slow, but in some cases enormous enlargements have developed within a few years

The blood picture is not usually altered in bancroftian filariasis Eosino philia is frequently present but probably in most instances is related to con

CLINICAL SYMPTOMS

In some endemic areas such as Fiji (O'Connor 1923) more than 70 per cent of the population has been reported infected with W *bancrofti* The infected individuals can be conveniently placed under two categories (1) persons positive for microfilariae usually upon blood examination and (2) persons showing manifestations of filarial disease i e elephantiasis The majority of the first group are symptomless while the majority of the second group do not show microfilariae in the peripheral blood

Prior to World War II observations on the clinical manifestations of bancroftian filariasis were largely related to native populations or Europeans of long residence in endemic regions among whom the earliest signs and symptoms were difficult to trace It was generally held that one or many more years had to pass before a demonstrable infection (microfilariae in the blood) could become clinically manifest However during the recent war a great number of cases were reported among military forces in which the onset of symptoms appeared within a few months after arrival in highly endemic areas an insufficient time for the parental parasites to have attained sexual maturity

The symptoms of bancroftian filariasis can be divided into inflammatory and obstructive (O Connor and Hulse 1935) The effects of inflammation are the first to appear and these may include lymphedema lymphangitis lymphadenitis funiculitis epididymitis orchitis filarial fever myositis and abscess Obstructive phenomena are the result of progressive inflammatory reactions They include lymph varix chyluria hydrocele and elephantiasis

The early signs and symptoms of bancroftian filariasis are both vague and variable but attacks of lymphedema lymphadenitis and lymphangitis of one form or another are at present considered cardinal signs of the disease in endemic areas The initial attacks may appear without warning and without apparent cause but sometimes develop following unusual exertion or exposure Lymphangitis in bancroftian filariasis appears to be characteristically retrograde The local symptoms are usually associated with varying degrees of generalized malaise pain numbness fatigue and slight rise of temperature (' filarial fever) At the height of a severe attack the entire arm or leg may become red tender and painful but within the affected extremity there may be one or more areas 'focal spots where the pain is especially severe Both living and degenerate parasites have been found in biopsy material removed from such areas These symptoms in foreign residents may be complicated by psychic trauma particularly fear of impotence or sterility (Zeligs 1945) The initial attacks usually cease spontaneously after a few days but tend to recur after shorter or longer intervals

In the obstructive phase of bancroftian filariasis lymphatic dilatation without rupture leads to lymph varix Lymph varices or varicose glands commonly occur in the skin particularly on the abdomen legs or arms in the groin in the scrotum the spermatic cord and in the abdominal lymphatics around the kidneys and those of the bladder wall Hydrocele commonly oc

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ig °67 —Elephantiasis of both legs of 45 years durat on attribute l to bancroftian filariasis in a on an 70 years ol l A l ritisl (u nea case Photograph by T H Wel er)



g °68 —1 l phant as s of the scrotum and legs attributed to bancroft an filariasis Britisl Guinea case (From Romiti, 1930)

DIAGNOSIS

The absolute diagnosis of bancroftian filariasis is usually made on finding the characteristic microfilariae in the blood When obtaining blood for examination, the phenomenon of periodicity *should be considered* Both day and night specimens should be collected It should also be remembered that microfilariae might not be present in the peripheral blood of many cases showing suggestive signs and symptoms in both early and advanced phases of infection, and that, therefore, negative findings do not necessarily exclude the diagnosis of filariasis Conversely, *the presence of microfilariae does not necessarily imply filarial disease*

1 Demonstration of Parasitism*

For the examination of blood for microfilariae, 6 or 8 large drops of blood are allowed to drop from the tip of the finger onto an ordinary clean slide and are evenly spread, before clotting, over the surface of the slide The blood films are dried in a level position, protected from insects and dust, but freely exposed to the air They are then dehemoglobinized in water When laking of the hemoglobin is complete, the slides are examined while still wet under low power of the microscope The microfilariae, if present, appear as glistening objects and are readily distinguishable

For morphologic study and identification of the microfilariae, the dehemoglobinized preparations may be stained with steaming Delafield's hematoxylin for 5 minutes and then washed with tap water They should then be differentiated momentarily in acid alcohol, washed again in tap water until blue, dehydrated in absolute alcohol, cleared in xylol, and mounted in Canada balsam, Clarite "x" (thermoplastic hydrocarbon resin, a product of the Neville Co , Pittsburgh, Pa), or any other satisfactory mounting medium

If this method fails to reveal infection, further search for microfilariae should be made by using a method which will concentrate them For such examination about 10 c c of venous blood are [illegible] minute [illegible] for immed[illegible] The concentration method should be used in the examination of chylous urine for microfilariae

Search for adult parasites in biopsy material is not recommended as a routine diagnostic procedure Adult worms are usually found in not more than 30 per cent of the cases The histopathologic changes within the node are suggestive but not specific for bancroftian filariasis Sporadic elephantiasis in temperate climates shows most, if *not all, the pathologic changes* associated with elephantiasis in filariasis Finding these changes usually has been considered confirmatory of the diagnosis in persons known to have been exposed to infection and in whom clinical symptoms are present, but actually it calls for further careful search of the worm in the excised material and for further search of *microfilariae in the blood*

2 Diagnosis Based on Clinical Manifestations

Frequently the diagnosis is made upon the presence of certain characteristic symptoms when they are noted in natives or foreign residents in endemic areas These symptoms are usually *referable to the early stages* and include lymphangitis, lymphedema, lymphadenopathy, myositis, and some

*See also Chapters 68 72 and 73.



Fig 267 —Elephantiasis of both legs of 45 years duration attributed to bancroftian filariasis in a woman 70 years old A British Guinea case (Photograph by T H Weller)



Fig 268 —Elephantiasis of the scrotum and legs attributed to bancroftian filariasis British Guinea case (From Romiti 1930)

DIAGNOSIS

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*See also Chapters 68 7" and 73

nes abscess There is however considerable disagreement among authori s on just what should be included under signs and symptoms of ban oftian filariasis Lymphangitis lymphadenitis lymphedema and particu rly permanent enlargement of the epitrochlear gland are considered by uxton (1928) and others to be the earliest positive signs of the disease engar (1938) however excludes the presence of enlarged glands lymphad itis and abscess because he could not determine to what extent they rep sented filarial disease but he includes elephantiasis lymph scrotum hydro le and lymphangitis particularly retrograde lymphangitis Buxton re rded hardness or enlargement of the testicle and epididymis and the pres ice of hydrocele as manifestations of bancroftian filariasis but finding it fficult to define the boundary between a normal testicle and epididymis and ie that was enlarged or fibroid he concluded that the male genitalia do not rovide useful physical signs in the diagnosis of filariasis Recently Webster 1946) from a study of case histories of 80 adult white persons with an aver ge duration of residence of 26 years in the Samoan Islands and showing signs id symptoms of bancroftian filariasis concluded that the mere presence of alpable axillary inguinal or epitrochlear glands is of little value in the diag osis in areas where bacterial infections of extremities are extremely com on

During World War II 10 421 cases of bancroftian filariasis were re orted among United States Navy personnel following service in the South acific area particularly in the Samoan Islands (Coggeshall 1946) The di gnosis in most of these cases was based upon (1) the presence of a transient etrograde lymphangitis localized lymphedema or lymphadenitis (2) service ading to exposure to infection and (3) a positive reaction to an intradermal st

To evaluate the importance of lymphadenitis in filariasis a careful phys al examination with particular reference to the presence of palpable lymph odes was made on 200 men of the above group with a clinical diagnosis of ancroftian filariasis 271 patients with malaria and on 98 men who had not een in tropical areas The data obtained from this study showed no signifi ant differences either in the number of men with demonstrable adenopathy r in the average number of nodes in any particular area Patients in the verseas groups had larger nodes than those in the control group which dif erence could be accounted for by the existence of active fungous infections n the overseas group Although lymphadenitis is usually considered to be he most frequent clinical manifestation of bancroftian filariasis in the above tudy it could not be used as a diagnostic criterion

There is close agreement among the authors that lymph varix chyluria nd elephantiasis are usually indicative of bancroftian filariasis in the later tages when occurring in natives and foreigners having had prolonged resi lence in an endemic area

3 Immunologic Tests

Various skin tests have been employed in the diagnosis of filarial infec tions The number of positive intradermal responses following the use of (1)

Dirofilaria immitis and (2) *Litomosoides carinii* (filarial parasites of the dog and the cotton rat respectively) antigens in suspected cases of filariasis led to the conclusion that this test was of diagnostic value (Taliaferro and Hoffman 1930 Fairley 1931 Culbertson et al 1945 Michael 1944) Later applications of these tests however gave irregular and uncertain results False positive reactions are believed due to cross sensitivity, i e a helminth group reacting factor from nematode infections other than filarial worms (Bozicevich and Hutter 1944 Wright and Murdock 1944 Saunders et al 1946) and to immune responses produced by infective filaria larvae of lower animals (Augustine and Lherisson 1946) Unfortunately immunologic tests at present cannot be relied upon for final decision in the diagnosis of filariasis

The only positive way of making a diagnosis of bancroftian filariasis is by identification of the infecting parasite either adult worms or microfilariae The recognition and correct diagnosis of this disease in the absence of demonstration of the parasite is usually difficult and requires detailed study Lymphadenopathy lymphedema and lymphangitis should always suggest the possibility of bancroftian filariasis when occurring in persons living or having lived in endemic countries Of these the commonest and most characteristic if not specific initial manifestation of the disease is an acute transient retrograde lymphangitis

TREATMENT

There is no accepted chemotherapy of bancroftian filariasis At the present time antimony compounds Neostibosan (Culbertson et al 1945) and Anthiomaline (Brown and Thetford 1946) hold the highest promise but still remain in the experimental stage According to Brown and Thetford (1946) patients treated with Anthiomaline experienced a marked microfilaria reduction which persisted for at least 2 years and some patients became microfilaria negative Patients treated with Anthiomaline showed no evidence of inflammation lymph stasis or other manifestations which might be expected to develop following the death of adult parasites and microfilariae and the concurrent release and absorption of toxic material The toxicity of these compounds should be further investigated before they can be recommended for general use

Santiago Stevenson et al (1947) obtained highly favorable results including rapid disappearance of microfilariae from the blood stream following oral administration of 1 diethyl carbamyl 4 methyl piperazine dihydrogen citrate (Hetrazan) The drug was administered orally 3 times daily before or after meals or every 8 hours The individual dose varied from 0 5 mg to 2 mg per kilogram of body weight and the number of days during which treatment was given varied from 3 to 21 days The drug is reported to have been well tolerated in all of the 26 cases treated More recently Hewitt et al (1950) reported a reduction in total microfilariemia up to 99 6 per cent in 65 patients treated with various doses of Hetrazan and re examined 1 year later The microfilaria positives in this group were reduced by 79 4 per cent No disturbing systemic reactions occurred during treatment

times abscess. There is however considerable disagreement among authorities on just what should be included under "signs and symptoms" of bancroftian filariasis. Lymphangitis, lymphadenitis, lymphedema and particularly permanent enlargement of the epitrochlear gland are considered by Buxton (1928) and others to be the earliest positive signs of the disease. Iyengar (1938) however excludes the presence of enlarged glands, lymphadenitis and abscess because he could not determine to what extent they represented filarial disease, but he includes elephantiasis, lymph scrotum, hydrocele and lymphangitis, particularly retrograde lymphangitis. Buxton recorded hardness or enlargement of the testicle and epididymis and the presence of hydrocele as manifestations of bancroftian filariasis, but finding it difficult to define the boundary between a normal testicle and epididymis and one that was enlarged or fibroid, he concluded that the male genitalia do not provide useful physical signs in the diagnosis of filariasis. Recently Webster (1946), from a study of case histories of 80 adult white persons with an average duration of residence of 26 years in the Samoan Islands and showing signs and symptoms of bancroftian filariasis, concluded that the mere presence of palpable axillary, inguinal or epitrochlear glands is of little value in the diagnosis in areas where bacterial infections of extremities are extremely common.

During World War II 10,421 cases of bancroftian filariasis were reported among United States Navy personnel following service in the South Pacific area, particularly in the Samoan Islands (Coggeshall 1946). The diagnosis in most of these cases was based upon (1) the presence of a transient retrograde lymphangitis, localized lymphedema, or lymphadenitis, (2) service leading to exposure to infection, and (3) a positive reaction to an intradermal test.

To evaluate the importance of lymphadenitis in filariasis, a careful physical examination, with particular reference to the presence of palpable lymph nodes, was made on 200 men of the above group with a clinical diagnosis of bancroftian filariasis, 271 patients with malaria, and on 98 men who had not been in tropical areas. The data obtained from this study showed no significant differences either in the number of men with demonstrable adenopathy or in the average number of nodes in any particular area. Patients in the overseas groups had larger nodes than those in the control group, which difference could be accounted for by the existence of active fungous infections in the overseas group. Although lymphadenitis is usually considered to be the most frequent clinical manifestation of bancroftian filariasis, in the above study it could not be used as a diagnostic criterion.

There is close agreement among the authors that lymph varix, chyluria and elephantiasis are usually indicative of bancroftian filariasis in the later stages when occurring in natives and foreigners having had prolonged residence in an endemic area.

3. Immunologic Tests

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Wuchereria Malayi (Brug, 1927) Rao and Maplestone, 1940

Wuchereria malayi was discovered in 1927 by Leichtenstein in the Dutch East Indies Leichtenstein had failed, after numerous attempts, to infect *Culex quinquefasciatus* and other culicine mosquitoes with microfilariae of the area Noting the absence of acute forms of the disease, although elephantiasis of the leg was common, it occurred to him that he might be dealing with a new species of filaria Brug (1927) examined Lichtenstein's material, found morphologic characteristics distinct from bancroftian microfilariae, and proposed the name *Filaria malayi* for the parasite The parental worms were first described and discussed by Rao and Maplestone *(1940)* and later studied by Bonne, Lie Kian, Joe Molenkamp, and Mreyen (1941) The adults were found to be morphologically similar to the adult of *W bancrofti*, and they are also parasites of the lymphatic system

W malayi appears to be strictly oriental in geographical distribution It is known to occur in the Federated Malay States, Sumatra, Java, Ceylon, parts of India, Indo China, and in northeastern Chekian Province of China It is often the dominant species of a given region and, whereas *W bancrofti* characteristically occurs in villages and towns, *W malayi* occurs typically in rural districts along river or forest settlements

Elephantiasis of the feet and legs is characteristically associated with *W malayi* infection The genitals and upper extremities are rarely involved as in bancroftian filariasis The microfilariae show nocturnal periodicity, but do not disappear entirely from the peripheral blood during the daytime They resemble bancroftian microfilariae but are identified by the presence of two distinct nuclei in the tip of the tail (Fig 262) Mosquitoes of the genus Mansonia, subgenus Mansonioides, are the principal vectors, particularly *Mansonioides annulifera* These are nocturnal feeders and are most active during the evening from 7 to 9 o'clock

Recently, extensive studies have been made on the control of filariasis in India, particularly in Travancore, where *Microfilaria malayi* is chiefly concerned (Sweet and Pillai, 1937, Iyengar, 1938) It was demonstrated by these investigators that the presence of a floating plant *Pistia stratiotes,* is essential for the breeding of Mansonia The female mosquito does not ordinarily lay eggs except on the leaves of Pistia and the larvae being structurally adapted to obtain their supply of oxygen from the air cavities in the root, are not capable of living apart from this particular plant

In experimental areas the clearance of ponds and tanks of Pistia markedly reduced the incidence of Mansonia mosquitoes and checked further spread of the infection Pistia plants can be cheaply and *effectively removed by hand* Here we have an excellent example of the *suppression of a mosquito borne* disease by a strictly limited species control of the carrier

Loa Loa *(Cobbold, 1864) Castellani and Chalmers 1913*

Loa loa is a relatively important filariid species Infection with it is frequently associated with acute inflammatory responses and transient edematous swelling in various parts of the body known as "Calabar swellings"

Loa loa is indigenous only in tropical West Africa and along the Congo River and its tributaries It is noted occasionally in other countries among Europeans and Americans particularly missionaries who have lived for some time in the endemic areas

Palliative measures with elevation of the affected part are usually recom nded for the immediate treatment of acute inflammatory attacks but auser (1945) and Coggeshall (1946) did not find heat cold massage or frared rays to affected parts beneficial Rest usually affords relief Follow g removal of the patient afflicted with early filariasis from the endemic area favorable surroundings the disease soon runs a self limited course before tual evidence of parasitism can be demonstrated Bancroftian filariasis is ldom fatal Sulfonamide drugs are recommended in the treatment of filarial mphangitis complicated by streptococcal or staphylococcal infection Pres re bandages are recommended in early elephantiasis of the legs (Knott 38) The bandaged leg must be exercised to prevent cyanosis The large brotic tissues of advanced elephantiasis have been frequently removed suc ssfully by surgery (Auchincloss 1930 Torgerson 1930 del Toro et al 30 Romiti 1930 Knott 1932)

PREVENTION AND CONTROL

In view of the fact that the parasite is transmitted solely through the tes of mosquitoes its prevention is primarily one of mosquito control *Culex uinquefasciatus* which is world wide in its distribution and which is probably e commonest vector of bancroftian filariasis is essentially a domestic mos uito It breeds near dwellings in cisterns rain barrels discarded tin cans wage drains and ditches Tight screens and gauze coverings will prevent osquito breeding in cisterns vats and rain barrels Discarded pots tins d other utensils should be buried or destroyed and drains and ponds kept ear of vegetation in order to effect proper mosquito control All breeding aces should receive weekly treatment with larvicides In the Oceanic lands where *Aedes scutellaris pseudoscutellaris* is the most important vector ttention must be centered on discarded cocoanut husks and shells natural d artificial cavities in trees tin cans and other possible containers of clean ater O Connor (1923) observed that the Pacific rat makes breeding places r this mosquito in trees by gnawing and gutting young cocoa pods In ueensland Australia *Anopheles amictus* is an efficient vector of bancroftian lariasis

Factors which favor endemicity of bancroftian filariasis are known to ary greatly not only in different countries but also in different nearby lo alities within an endemic country Thorough analysis and understanding f these factors are essential before effective control can be realized The lentity of the mosquito and knowledge of the conditions which permit it to ourish are of first importance in control of the disease in mankind Better ousing conditions screening of doors and windows and the use of bed nets re often recommended but such measures although effective if properly arried out are seldom applicable in native villages At the present time the nly effective measures against bancroftian filariasis are those which can be pplied directly against the mosquito vector

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The parental worms are parasites of the subcutaneous tissues, particularly of the arms, legs, and head and have been found in the peritoneum. When fully mature, they characteristically migrate and frequently appear beneath the skin in various parts of the body. Because of this habit they have been observed more often than any other adult filarial species infecting mankind.

The male worm measures from 25 mm to 35 mm in length and about 0.35 mm in breadth. The female varies considerably in length up to 70 mm and is about 0.5 mm in breadth. The average length is about 50 mm. The cuticle is embossed with wart like projections except at the anterior extremities of both sexes and at the tail of the male which areas are smooth. The microfilariae show diurnal periodicity, appearing in the morning and disappearing at about 9 o clock in the evening. They are sheathed forms. In stained films, they appear somewhat stiff and angular whereas microfilariae of *W. bancrofti* assume more sweeping and graceful curves (Fig 262)



Fig 269.—Loaiasis. Calabar swelling of right wrist. (From Guy Cohen and Jacob 1943.)

Loa loa is transmitted to man by mangrove flies *Chrysops dimidiata* and *C. silacea*. The development of the parasite in these hosts is similar to that of other filariid worms.

Development of the worm in man is slow. It has been estimated that the life span of the adult worm is about 15 years. Calabar swellings, which are generally regarded as allergic responses may reappear for years in the absence of other evidence of loaiasis. Aside from the itching and irritation caused by migrations of the adult worms and the transient subcutaneous swellings, apparently no damage is done and the patient usually enjoys good general health. There is no effective chemotherapy known. The adult parasites may be readily extracted through a small incision when they appear in the conjunctiva.

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Biologic Characteristics

The adult *Onchocerca volvulus* lives in the encapsulated onchocercoma located in t subcutaneous tissues of the body Within such lesions the parasites are *found intricate* coiled They give rise to microfilariae which find their way into the skin It is not unusu to find more than one male worm associated with one female in a solitary nodule (San *ground, 1938)*

The microfilariae are found free in the connective and subcutaneous tissue, in the lymp spaces, in all parts of the eye, particularly in the *superficial layers of the cornea, and* on accidentally in the deeper parts of the body

The size of the adult specimens is variable, from 100 mm to 700 mm long accordin to several authors



Fig 270 —Microfilariae from the lymphatic spaces of the skin

HOST

Onchocerca volvulus has only one definitive host—man The intermediate hosts are *Simulium ochraceum, S callidum, S metallicum* in America, and *S damnosum* and *S neavei* in Africa

LIFE CYCLE

The ovoid or elliptical eggs develop in the uterus of the filarial worm and contain an embryo When the larvae reach maturity, they are released in great numbers At this time they migrate to the subcutaneous tissue, through the intercellular spaces

Infection of the flies takes place through contamination of the biting parts The route of migration of the infective larvae in the insect is largely conjectural (Sandground, 1938)

Hoffmann (1930) traced the development of microfilariae in *S callidum* and showed that the larvae, 68 hours after being ingested by the fly, had developed into sausage shape He divided the development cycle into 4 stages first, passage of microfilariae to the stomach and then to the thoracic muscles of the fly, second the shortening process, third, the "sausage shape", and fourth the development into a mature worm like larva

CHAPTER 40

ONCHOCERCIASIS

Luis Benitez Soto and Amelia Samano Bishop

CAUSAL AGENT

Onchocerca Volvulus Leuckart 1893

Synonyms —*Microfilaria nuda* Rodenwaldt 1914, *Onchocerca volvulus caecutiens* Brumpt 1919

Onchocerciasis is caused by the filarial worm *Onchocerca volvulus* Leuckart Several species of simuliid flies play a part in the transmission of the disease

HISTORY

Onchocerca volvulus Leuckart was first described by Leuckart in 1893, he found the parasite in a native of the Gold Coast, Africa Blacklock, in 1926, observed the metamorphosis of the larval forms in the African vector *Simulium damnosum* and also found the larvae in the skin of African natives In America, Robles, in 1915, found the filariae in onchocercomas of the scalp in inhabitants of the Pacific slopes Hoffmann, in 1930, for the first time traced the development of the microfilariae in *S callidum* Ochoterena (1930) demonstrated the microfilariae in an eye excised from a blind patient

Manifestations of American onchocerciasis were described by several investigators Brumpt (1919) considered the American filaria a new species because of the slight variations in the size of the males, the arrangement of the papillae, and the distribution of the onchocercomas in the body The observations of Sandground (1934), Fulleborn, and others, and more recent studies of Caballero (1945), have definitely shown that the African and American parasites belong to the same species *

MORPHOLOGY OF THE ADULT PARASITE

The worms are opalescent, white, with transverse striations and annular thickenings, head bluntly rounded, alimentary canal straight, with subterminal anus The tail of the male is markedly curved and has a slightly bulbous end, perianal and caudal papillae in variable numbers, spicules unequal The posterior end of the female is bluntly rounded, vulva at the anterior part of the body, at times postesophageal This species is viviparous

THE MICROFILARIAE

The microfilariae vary in size There are small and large forms The small forms are 0 15 to 0 287 mm in length by 5 to 7 microns in breadth, the large forms are 0 285 to 0 360 mm in length by 6 to 9 microns in breadth according to some authors The anterior end is enlarged and bluntly rounded, posterior end abruptly narrowed with sharply curved extremity, no cells with deeply staining nuclei in the terminal part of the body The microfilariae show coiling or twisting movements

legs, and if the shade afforded by the long grass is favorable, they attack the face, neck, and shoulders As a rule the bite is low on the body, mostly below the knees, in Africa, because of the scarcity of overhead shade

Morphology of the Vectors

The Genus Simulium—The Simuliidae are 1 to 6 mm in length, have a stout body, and short legs The mouth parts are formed for piercing and sucking The thorax has a characteristic "humped" appearance The head has 11 jointed antennae with hairs, palpi are 4 jointed

The eyes are contiguous in the male and distinctly separated in the female Wings are broad and iridescent, with well developed veins, legs with hind basitarsus produced apically, second hind tarsus with dorsal incision

Life Cycle of the Vectors

Oviposition and Eggs—It has been found that only the female flies attack man A blood meal *appears to be a necessary factor in the development of the ova (Jobbins Pomeroy,* 1916, Wu, 1931, and Cameron, 1922) At least 2 days must elapse after the blood meal before the development of the egg begins When the females are ready to lay their eggs, in favorable weather in the evenings or before sunset, they gather in large swarms and fly toward the breeding places

The larvae of the Simuliidae can usually be recognized by the bending of the body in a "U" or "J" shape when drawn aside from the water (O'Kane, 1926) An ideal breeding place for the larvae of the pupae is in streams with rocky bottoms and abundant aquatic vegetation (Vargas, 1945) When the larvae are ready to pupate, they seek protected places such as the underside of stones, stems, and leaves

The duration of the larval period of the Simuliidae varies widely in some species 4 to 7 weeks During this time the larvae undergo 6 molts

Puppation takes place in the larval habitat The larvae spin their silken cocoons, which are conical, shaped like an open pocket, or boat shaped, as in *S damnosum* The cocoons are flat on the attached side and convex on the free surface

The species can be easily recognized by dissection of the mature pupa (Hoffmann, 1931) The color of the legs is almost characteristic in the case of *S metallicum* and *S callidum*, in *S ochraceum* the specific black color appears rather late Hoffmann (1931) and Edwards (1939) consider the structure of the respiratory organs to be of diagnostic value *S ochraceum* and *S callidum* are provided with respiratory appendages with 8 lobes, *S damnosum* with 11 short, thick, and very unequal lobes, and *S metallicum* presents a respiratory organ with just 6 long branches arising from 3 main stems, each of which divides into 2 simple branches

The pupal period varies according to the different species and the weather, it is longer in cooler weather and generally takes 3 to 7 days

The duration of the life cycle varies according to the different species of Simuliidae and to the altitude The observations of several investigators have shown that it varies from 3 to 15 weeks (Needham, 1901, Verdat, Johnsen, 1903, Jobbins Pomeroy, 1916, Emery, 1914) Vargas (1945) has obtained development of several species, among them *S callidum* and *S metallicum*, at a water temperature of 14° C, the time required for the entire cycle was 3 weeks

Mechanism of Transmission

It has been suggested (Vargas, 1942) that when the insect introduces the mouth parts into the skin, the fly injects a certain amount of saliva that exerts a chemotactic influence, causing a concentration of the microfilariae near the surface of the skin for as long as 18 minutes while the Simulium ingests numerous microfilariae

The microfilariae develop especially in the dorsoventral muscles of the fly (Vargas 194) and during their growth one or more ecdyses probably take place (Blacklock 1926) The infective forms of microfilariae are found in the head of the fly after a period of 10 days or longer

VECTORS

There are 5 species of simuliid flies involved in the transmission of American and African onchocerciasis *Simulium metallicum* Bellardi 1859 *S callidum* Dyar and Shannon 1927 *S ochraceum* Walker 1860 and *S neavei* Roubaud 1915 in Africa and *S damnosum*

Robles (1919) in America and Dry in Africa alluded to the possibility of a Simulium as transmitter of onchocerciasis In 1926 Blacklock in Sierra Leone observed the metamorphoses of the larvae of *O volvulus* in the transmitter *S damnosum* and reported the presence of microfilariae in the intestine of the fly Later (1930) he found the microfilariae in the thorax of flies which had previously bitten infected natives

In America Hoffmann 1930 also eluded the occurrence of microfilariae in the stomachs of *S callidum* and *S ochraceum* A short time later Hoffmann was able to observe localization of the larvae in the thoracic muscles of both species Bequaert (1928) in Liberia confirmed the observations of Blacklock and Hissette (1932) in the Belgian Congo found the stages of development in *S damnosum* and *S neavei* Strong 1931) in America verified Hoffmann s findings

Flies of the genus Simulium are commonly known as jejenes in Mexico Central America and Argentina Under this name some other groups are also included (Vargas 194) such as Ceratopogoninae and Phlebotomus In the onchocercal regions of Chiapas (Mexico) the transmitters are known as mosquitos azanes or moscos de caf In the United States they are usually called buffalo flies black flies or turkey gnats and in Central Africa jinj

Habitat of the Vector

According to Hoffmann the African and American transmitters differ little in their biologic manifestations The American vector insects are not joined to the dampness rather of the virgin forests Here they seem to seek shelter in shady places They live at altitudes of 2 000 to 4 00 feet above sea level

The adult flies live in the forest early in the morning and migrate to the less dense woods near the farms In the early morning hours the Simulium bites the upper part of the body (Hoffmann) Later when the sun rises however the black flies take refuge in shady places in coffee plantations and neighboring forest At this time the females seek the moisture of the ground so that workers in plantations are frequently bitten on the legs (Hoffmann 1931)

It becomes apparent that not all species of the Simulium attack the same regions of the human body *S ochraceum* bites principally the head and *S metallicum* and *S callidum* the lower parts of the body These vectors persist throughout the entire year but are more abundant from September to January or February

The African species *S damnosum* and *S neavei* live at elevations of 1 000 to 1 500 feet above sea level They are chiefly confined to hilly countries covered with grass and bushes near streams and rivers

Blacklock (1926) stated that the Simuliidae do not bite earlier than 6 00 A M and that in the middle of the day the fly would not go far in order to bite not even 5 yards as a rule The flies were found biting however in bright sunny weather at any hour of the day provided they had only a yard or two to go from their shelter On dull or cloudy days without rain they bite freely at any hour of the day The flies especially choose shaded portions of the

first year of the development of the disease at a coffee plantation recently invaded St et al (1934) observed lesions in 4 children less than 10 months old

The inculation period may be considered as between 3 and 9 month

Cutaneous Lesions

The following cutaneous lesions have been described in American African onchocerciasis onchocercoma mal morado erisipela de la cost edema elephantiasis pruriginous and xerodermatous conditions of the s The latter were mentioned by Strong (1938) especially among diseased individuals from the Province of Lusambo but we have also observed them America

Onchocercoma

Basing his opinion on the evidently granulomatous histologic structure the lesions Benitez Soto (1936) proposed the name onchocercoma ' for cutaneous lesions which had formerly been called by other workers cyst tumors ' nodules or fibromata

Location of the Onchocercoma—The location of the onchocercoma var according to the geographic regions Generally in Africa the lesions are si ated on the trunk

Appelmans (1935) states that in the Belgian Congo onchocercomas frequently found near the costal region the scapula shoulders iliac cres knees and elbows

In America these onchocercomas are found especially on the head Stro (1938) mentions Blacklock s findings in Africa of 8 patients who had t onchocercoma on the head but this was exceptional

In 95 per cent of African cases of onchocerciasis the onchocercomas a situated on any part of the body but not on the head according to several i vestigators mentioned by Strong

In Guatemala Robles (1919) found 99 per cent of the cases of onch cercoma localized on the head

Benitez Soto in 1945 at the hospital in Huixtla Mexico found th of 23 patients with onchocerciasis 22 had numerous onchocercomas on t head and the only one who had no lesions had *mal morado* In other word of 22 patients observed at random all either had or had had onchocercomas c the head with or without other lesions on the trunk and extremities that i 100 per cent of the cases of onchocercoma showed cephalic localization

Finally in African onchocerciasis in the majority of cases the situatio of the onchocercoma is not cephalic as opposed to the American which l calizes principally on the head

In American onchocerciasis the cephalic onchocercomas show some pr dilection for temporal parietal and occipital regions and certain cases pre fer also the *anterior* and superior iliac spine

Cause of the Location of the Onchocercoma—It has been said that the lo cation of the onchocercoma depends upon the site of the bite of the fly as as

The microfilariae reach the alimentary canal of the fly and then migrate to the thoracic muscles, where further development takes place into infective forms, which then go to the head and finally to the labial structures to escape when the insects bite human beings

The bites of the different black flies vary in severity Gibbins (1938) considers that the bite of *S damnosum* is perhaps the most severe Balfour (1906) states that "the insect bites fiercely and is a veritable terror in certain parts of the Sudan" The bite of the American transmitter *S ochraceum* does not seem to be very annoying from the beginning of the attack. The bites of *S callidum* and *S metallicum* are very painful. Subsequently a papular lesion develops, followed by edema, pruritus, and hemorrhage which may last for several days

The effects of the bites vary according to individual susceptibility, sometimes the lesions may cause fever



Fig 271 — Sausage stage of a microfilaria in the thoracic muscles of a fly (After Hoffmann)

CLINICAL SYMPTOMS

The adult *O volvulus* or the microfilariae produce in the human organism a number of clinical manifestations which have received the name "onchocerciasis" The most frequent manifestations occur in the skin and in the eyes, and these make up the most characteristic objective signs of the disease (Benitez Soto, 1936)

Onset

It is very difficult to recognize the beginning of the disease because the precise moment of the bite of the infective fly is not known

Robles (1919) considered the incubation period to be about 3 months, including the appearing of the onchocercoma and the other manifestations He based his opinion on observations of people who had come from uninfested places and had established quarters in onchocercal regions, and who showed characteristic manifestations 3 months after arrival Hoffmann and Vargas (1931) believe that onchocercomas appear 8 or 9 months after the infection These authors base their opinion on finding such lesions in children 9 months after birth. They were also able to observe the clinical manifestations which appeared within the

Size—Darriba (1935) believes that the onchocercoma is generally a little larger in African onchocerciasis than in the American type Benitez Soto (1936) stated that the size of the onchocercoma of American onchocerciasis is variable and commonly proportional to its age

Some onchocercomas vary in size from several millimeters to that of a pigeon egg Appelmans (1935) calls attention to the fact that these very small onchocercomas might be overlooked by the physician

Shape—The shape is usually globulose according to Benitez Soto with slight modifications—ovoid moniliform, and pear shaped This author considers such modifications to be due to mechanical action caused by hardness of the anatomic parts with which they come in contact

Color—The color is uniformly pinkish white

Hardness—Onchocercomas are very hard almost cartilaginous in some cases with the appearance of exostosis especially when they are not movable Appelmans (1935), in Leopoldville found onchocercomas so hard that they simulated juxta articular nodules



Fig 273—Different sizes of onchocercomas

Mobility—Mobility varies but commonly *they are only slightly movable* In some sites the limited mobility and the situation near an osseous plane may cause them to resemble exostoses

Sensitiveness—Both American and African types *are genuinely painless*

Appearance of the Sections—Thin sections present a characteristic aspect (Benitez Soto 1936) which consists of the presence of bands and empty elliptical circular, or irregular spaces

Mal Morado

The name "mal morado" is given to *a number of cutaneous manifestations* with chronic evolution caused by the *O volvulus* Robles (1919) described such chronic states of the disease, emphasizing the "absolutely typical livid greenish *color" of the face*

Fulleborn (1923), in examining a boy in Hamburg who had come from the onchocercal region of Mexico found in the skin a blue greenish spot and

imed from the observations of Blacklock in Africa (cited by Strong et al 1934) and of Hoffmann (1930) in America Benitez Soto (1938) at that time believed that it is not possible to give a satisfactory explanation regarding the cause of the location of such onchocercomas

Number — Although the cause of the location of the onchocercomas is still an unsolved question this is not so of their number both in African and in American onchocerciasis Strong (1938) states that in Guatemala Mexico Sierra Leone Liberia and parts of the Belgian Congo the number of onchocercomas generally varies from 1 or 2 up to 5 or 6 although cases have been found with as many as 26 and 150 onchocercomas and with as few as only 1

Robles (1919) in Guatemala reported that the number of onchocercomas may vary from 1 to 17 and considered the presence of only 1 as very rare



Fig ° —Cephalic onchocercoma.

Benitez Soto (1945) showed the exceptional finding of 1 onchocercoma and the frequency of multiple onchocercomas varying in these cases from 4 to 8 We call attention to the fact that patients often presented a certain number of onchocercomas which were surgically removed A short time later new onchocercomas appeared and these were also removed the sum is estimated in these data

Strong (1938) believed that the great variation in the number of onchocercomas in different localities might have been partially explained on the basis of the number of times that the individual had been bitten by the infected Simulium

It is important to point out the lack of absolute symmetry in the location of the onchocercomas a fact that Robles (1919) had already observed he stated that the lesions are distributed at random

Munoz Ochoa (cited by Hoffmann, 19?5) says, with regard to Mexican onchocerciasis "the patient attacked by the filarial worm gradually loses his sight", further, "the main disturbances are in the vision, and at the end of the disease the patient becomes blind" Larumbe (1928) reports some disturbances that he observed, Pardo (1927) doubts whether ocular disturbances may suddenly cease after the removal of the onchocercoma In 1932, Silva published an article concerning the study, in 1925, of a patient from Guatemala who was afflicted with ocular disturbances Silva was able to see, in the vitreous body, a parasite that he thought was a filaria

Torroella (1931) clearly observed the living microfilariae in the cornea and anterior chamber Ochoterena (1930) described the eye lesions and reported the presence of microfilariae in sections of the organ.

Later Strong (1931) also described microfilariae in the eye In 1932 Hissette presented detailed clinical descriptions of eye disturbances in African onchocerciasis In 1935 Applemans reported the uniform distribution of microfilariae through the uveal tract Hissette (1932) stressed the remarkable frequency of ocular complications in numerous African regions

Torres Estrada (1942) suggested the possibility of observing microfilariae in the vitreous body by direct ophthalmoscopy



Fig 276—The arrow shows the xerodermatous auricle

Fonte Barcena (1945) described the conjunctival syndrome, and the same author, with Puig and Quiróz (1945) reported the results of their ophthalmologic investigations carried out in the onchocercal region of Chiapas Puig (1946) published an article with further details of the former work

The Onset—According to Hissette, onset is slow and occurs late in African onchocerciasis On the contrary, Torroella (1931) considers that the onset is rapid in American onchocerciasis The same authors state that the most characteristic phenomenon at the beginning of the disturbance consists of pain very much like the piercing of a pin, increasing during the day, especially during the hours of most intense light

Incidence and Other General Characteristics—*There was a time when it* was thought that ocular lesions were predominant in American onchocerciasis Numerous investigators have demonstrated that ocular lesions also occur in African onchocerciasis The authorities have not come to a common accord regarding the percentage of such lesions in onchocercal patients D'Hooghe

discrete edema In fact there are 2 principal symptoms of this syndrome a violaceous green color, sometimes light and a discrete hard edema of the skin which gives it a glossy aspect

Benitez Soto has observed that these symptoms are present in children as well as in adults and are the same for men and women but that they generally occur in the white race

The location of the disturbance is more evident in the face and neck than in other parts of the body Sometimes the palpebral regions swell so that a patient can hardly open the eyes In other cases the edema is marked in the auricle

In the more typical forms the swelling is hard especially about the face The eyelids the ears and the cheeks become thicker the skin appearing tense and glossy Some deformity of the auricle might take place but the interesting disturbance is the green violaceous color of the affected regions This color is not so intense as to be noticed immediately but is seen upon careful observation and occasionally it is associated with urticaria

The cutaneous disturbances are modified after some time by complications due to scratching

Investigations show microfilariae in the skin of these parts Histologic study reveals in them a discrete lympho plasmocytic infiltration with some eosinophiles

There is as yet no satisfactory explanation of the color of the skin edema of mal morado

Erisipela de la Costa

Robles (1919) gave the name erisipela de la costa to an acute condition of the disease characterized by edema of the face and neck marked edema of the eyelids and lips red tense skin shiny and painful in association with a rise in temperature of 39° to 40° C prostration convulsions and delirium Similar symptoms have been described for the extremities The description given by Robles is of an infectious type of erysipelas and several authors have questioned the filarial origin they have suggested that this is an allergic phenomenon or a real erysipelas caused by scratching the skin with a resultant secondary streptococcus infection of the skin leading to the typical erysipelatous lymphangitis This opinion seems to be correct because no typical cases of erisipela de la costa actually associated with onchocerciasis have been found

In short lesions described as an acute condition of the disease and called ' erisipela de la costa have not proved to be of onchocercal origin and it has been suggested that these are allergic or infectious conditions the latter produced by a streptococcus

Xerodermatous Conditions

According to Strong (1938) xerodermatous conditions are more common in African than in American onchocerciasis They are more frequent and more marked in cases of repeated edema especially in old cases Benitez Soto has

anatomic location of the lesions for we believe that it is somewhat artificial to divide them into stages because ocular manifestations have no regular or methodical development

Keratoconjunctivitis and Scleritis The patients complain of photophobia epiphora, burning sensations, or of foreign bodies Objectively it is possible to perceive blepharospasm punctate keratitis corneal and conjunctival vascularization, edema, and conjunctival pigmentation

The photophobia is more marked during the hours of increasing sunlight at midday, and is quite variable from one patient to another



Fig 278—Blepharospasm due to ocular onchocercal lesions

Epiphora Epiphora is a consequence of disturbances in the anterior chamber and is also variable in intensity The burning sensation and sensation of a foreign body are due to the inflammatory process and to the presence of microfilariae in the eye A slight or marked blepharospasm is sometimes observed especially during examination of the eye

Punctate keratitis is characterized by the presence of numerous punctations or round infiltrations about the superficial corneal margin which progress to the center while the oldest become vascularized As a result of the corneal infiltration the peripheral vascularization of the cornea at the place of greater disturbance which is generally discrete, sometimes gives rise to superficial vessels the "onchocercal pannus" of Hissette (1938) It may be so marked in the conjunctiva that it can present a triangular shaped sclero

(1935) reported 12 1 per cent Hissette (1938) found them very prevalent Giaquinto Mira Diaz and Estevez in Guatemala found about 40 per cent of ocular lesions

Fulleborn (1931) in Guatemala noted very rare eye disturbances Muhlens (1932) at La Granja Mexico found that 10 to 20 per cent of the patients had ocular disturbances Strong et al (1934) in Guatemala found 5 per cent of cases Hissette in Hebbo and Puig Fonte Quiroz (1945) in the onchocercal region of Huixtla Mexico found—in only a few observations—75 per cent of the same disturbances

Finally ocular disturbances are prevalent in both African and American onchocerciasis and vary in proportion according to the observers



Fig 277 Facies improperly called facies onchocercosa.

According to Figueroa Ortiz and co workers of 22 580 patients 8 083 suffered from ocular disturbances which is 33 88 per cent a very high percentage In spite of the high percentage of eye disturbances the scarcity of blindness is striking Among the same 8 083 patients 104 or 1 28 per cent were blind

The time between the onset of the disease and the beginning of ocular lesions according to Hissette (1938) is short, according to Puig Fonte Barcena and Quiroz (1945) it is 7 or 9 years

tions
(2)
and

The exudative type is not frequent but is characteristic and well defined It usually has crescent shaped short spaces, well marked, and composed of a serous layer, coagulated and granular within, which is an accumulation of erythrocytes lymphocytes, polymorphonuclear neutrophiles, fibrocytes, and histiocytes The lymphocytes are relatively abundant, the polymorphonuclears are scarce, the other cells are of a neutrophilic variety which sometimes undergo the transformation of the pyocyte, fibrocytes with vesicular nuclei are scarce At times the neutrophiles predominate and take the characteristics of pyocytes, and true microabscesses are formed

The granulomatous type seems to be the most interesting, it appears first and the adult types are derived from it

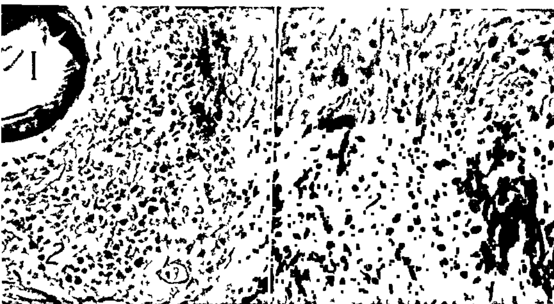


Fig 281 —Two sections of an onchocercoma. *1* A section of a filarial worm *2* a typical granulomatous tissue

It consists of cells and fibers The cells undergo a characteristic polymorphism, which might be of hematic or of connective tissue origin Elements of hematic origin are lymphocytes plasma cells, and polymorphonuclear neutrophiles and eosinophiles The elements of connective tissue origin are fibrocytes, histiocytes and giant cells The lymphocytes are abundant but with normal characteristics The polymorphonuclear neutrophiles have no definite arrangement and are isolated or in small groups Eosinophiles are rare Plasma cells are mixed with other cellular varieties or form small perivascular nodules Among the cells of the connective tissue group are young fibrocytes, almost embryonal, with large, round, and vesicular nucleus barely chromophilic

The histiocytes are numerous without distinct limits, with pale cytoplasm and vesicular nucleus, are isolated and form small groups within the mesh of a fine collagenous network, or are arranged in layers Giant cells may be ab

orneal base with the vertex toward the palpebral fissure pale reddish in color ore or less corresponding to the horizontal meridian of the eye

Fonte Barcena (1945) reports conjunctival pigmentation but this feature as not been frequently described This phenomenon is characterized by the rown color taken by the conjunctiva especially at the triangular region of ascularization Fonte Barcena (1945) states that the combination of the red olor of the blood vessels and the brown pigment constitute the characteristic marron color of the onchocercal eyes Benitez Soto has seen patients with ese symptoms he considers that the marron shade is just a shade of



Fig 9 Blindness due to onchocercal infection

brown The edema about the conjunctiva is not well marked and generally t is of little importance as a symptom of onchocerciasis Appelmans (1935) eported a deep congestion at the level of the limbus which is spread to the quator of the ocular globe as the sclerotic process is touched by the inflam natory process

Iritis Cyclitis and Chorioiditis Hissette (1932) as well as Appelmans 1935) in Africa Pacheco Luna (1919) in Guatemala Larumbe (1930) Tor oella (1930) and Puig Fonte Barcena and Quiroz in Mexico have confirmed he frequency of iritis in onchocercal patients and at times the more severe

sent if they are present the size is in inverse ratio to their age and varies considerably some are 20 to 30 microns while others measure 200 microns It is possible to find some small cells next to the large ones Round forms prevail but oval elliptical angular and long forms might be present The cytoplasm is very abundant homogeneous with 2 to 40 nuclei arranged as a morula These cells dwell in the fine collagenous fibers their density and distribution is very irregular

Adult The adult form may be of 2 varieties the adult proper and the fibrous

The adult form has the same cells as the granulomatous variety but the collagenous bundles are numerous with fibroblasts and fibrocytes in the spaces At times this tissue comes in direct contact with the filaria but com monly it is continuous with the internal surface of the fibrous capsule so that it resembles fibrous bands derived from the capsule

In the fibrous variety the same elements generally take part except that the abundance of collagenous fibers is remarkable

In large onchocercomas fibrillogenesis is very intense The blood vessels are very numerous in the granulomatous and less in the fibrous type com monly present is an endarteritis

Histogenesis According to Ochoterena (1931) onchocercomas are pro duced by a filarial worm stopping in a lymphatic vessel and by the centripetal fibrillogenesis Benitez Soto (1936) stated that unquestionably the parasite or its toxins or both predetermine the formation of such lesions There is an additional factor namely the presence of free fragments of the parasite

Cutaneous Lesions

Cutaneous lesions vary according to the region where they are present When they are xerodermatous the keratinization is exaggerated and the irreg ular detachment of the crust is well marked Microscopic examination shows congestion diffuse or perivascular infiltration with mononuclear cells at times with polymorphonuclear neutrophilic and eosinophilic leucocytes discrete fibro is and at times microfilariae Arroyo (1931) has described cases of atrophy of the Malpighian stratum with thinning of the interpapillary sites of the epidermal regions of the microscopic lesions or lesions of mal morado

The disturbances are more marked in the dermis The microfilariae are found in the lymphatic spaces of the connective tissue in different proportions but especially under the epidermal layer The more deeply they invade the ess often are they found Hoffmann (1930) considered that this was due to a positive phototaxis

The distribution and number of microfilariae are variable they are more abundant about the onchocercomas Furthermore in the connective tissue of he dermis a moderate or slight inflammatory process is present which con ists of cells such as fibroblasts lymphocytes plasma cells and some poly morphonuclear neutrophiles and eosinophiles arranged in small perivascular groups or in a diffuse manner

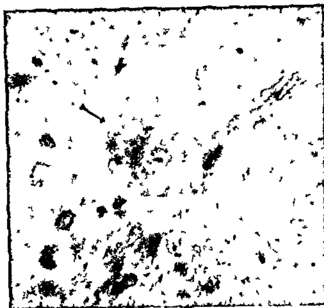


Fig 282—The arrow shows the giant cells of the onchocercoma.



Fig 283—Dense fibrous formation in an African onchocercoma.

Cornea.—Vascularization occurs near the periphery (Strong et al. 1934) with deposit of exudate about the sclerocorneal limbus and lympho-plasmocytic and monocytic infiltration (Hissette 1932). The corneal epithelium is irregular; there is infiltration in the stratum mucosum or stratum Malpighii with leucocytes and folding of Bowman's membrane (Ochoterena 1930) or its destruction in certain places.

Conjunctiva.—Strong (1932) believes that the lesions of the bulbar conjunctiva superficially near the cornea resemble those seen in the skin. Fonte Barcena (1945) has described a brown pigmentation corresponding to the palpebral sulcus.

Sclera.—According to Hissette (1932) the sclera is actually normal, but Puig (1946) states that Fonte Barcena believes that in some cases it undergoes the general process.

Iris.—Ochoterena (1930) states that the anterior endothelium is swollen and detached at some places and that there is edema and diminution of pigment; according to Hissette (1932) there are synechiae in the iridocorneal angle with reduction of the anterior chamber but without synechiae in the pupillary border of the iris; according to Puig et al. (1948) there occur edema, atrophy of the stroma and slight inflammation, together with alteration of the posterior pigmented epithelium and of the muscles.

Ciliary Body.—Appelmans (1935) reports atrophy in toto.

Choroid.—Congestion, edema and cellular infiltration have been observed in the choroid.

Retina.—In cases with lesions of the retina these are discrete and correspond to retinitis or hemorrhages (Hissette 1932).

Optic Nerve.—Scott (1945) reports atrophy in certain cases.

According to Rivetoll Noble (1947) everything points to the fact that the ocular lesions in onchocerciasis are of the chronic inflammatory type, not specific, and that they are similar to those produced by a foreign body.

Blood Changes

Studies to date reveal a slight anemia of the hypocythemic type (González Guzman 1930), and according to the same author, Benitez Soto (1930), Hoffmann and Vargas (1931) and Ruiz (1945), a marked eosinophilia. Benitez Soto (1930) reported 22.7 per cent eosinophiles and González Guzman 30 per cent. Ochoterena found 30 per cent in one count. Hoffmann and Vargas (1931) found a variation of 10 to 40 per cent. Ruiz (1945) found 15 to 40 per cent. This eosinophilia decreases as the onchocercal lesions disappear (Ruiz 1945).

EPIDEMIOLOGY AND ENDEMIOLOGY
GEOGRAPHIC DISTRIBUTION AND ALTITUDE

Onchocerciasis is a disease which occurs throughout well-defined areas. In America it is found in Mexico and Guatemala.* There are two zones in Mexico, one in the state of Chiapas and one considerably extensive zone in Oaxaca.

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*Recently another onchocerciasal infestation has been found in Venezuela. See footnote on p. 893

This infiltration is not in relation to the microfilariae There is not really a granulomatous character Arroyo (1931) and Mohammed (1931) believe that the intensity of the inflammatory process is in direct relation to the severity of the infestation and Strong et al (1934) considers susceptibility as a complementary feature Arroyo (1931) has described another lesion which consists of the thickening of the collagenous bundles of the dermis which consequently becomes thicker Strong et al (1934) believes that the inflammatory reactions described are a result of the irritation caused by the microfilariae and their movements or by the disintegration of dead microfilariae Arroyo (1931) supposes that it may be the response to a mechanical irritation which determines the presence of the microfilariae or the outcome of the soluble substances which they produce acting as chemotropic bodies



Fig 284 Section of skin from face in onchocerciasis Subepidermal microfilariae are visible

Ocular Lesions

According to Hissette (1932) and Appelmans (1935) the onchocercal eye is not modified microscopically However we have found that microscopically the ocular lesions are characterized by the presence of microfilariae in different parts of the eye and alterations of the histologic components of this organ Silva (1932) reported the observation in 1925 of a movable body in the vitreous humor which he thought might be a microfilaria This observation was made under doubtful circumstances as to the identification of the organisms which deprives it of value Torroella in 1931 reported the observation in vivo of microfilariae in the human eye Ochoterena (1930) found microfilariae in histologic sections of the eye and Strong (1931) several months later confirmed their presence in the conjunctiva iris and cornea Hissette (1932) affirms that the microfilariae are found in the conjunctiva sclerotic cornea iris ciliary body choroid anterior chamber and optic nerve Other authors later confirmed finding the microfilariae in vivo and in sections and have even suggested methods of observing them easily (Torres Estrada 1943) The number and location of the microfilariae are variable but they are commonly more numerous in the superficial parts in the connective tissues and at the slope of the iridocorneal angle

be made with the iris diaphragm partially closed Rapidly moving micro filariae are frequently seen by this method

When the skin gives negative results and ocular lesions point to the disease a similar technic can be used for the conjunctiva at times the results are positive

The best results are secured with skin taken near the onchocercoma and with pieces of superficial skin in which hemorrhage has not occurred The modus operandi consists of the use of a razor blade placed on the previously



Fig 785 —MacFie and Corson s technic for the investigation of microfilariae in the skin

disinfected skin holding between the forefinger and thumb of the other hand a portion of the skin The razor blade should be placed on this skin almost parallel to the surface in such manner as to raise a small flat fragment of the skin Further steps have been described above

We have tried another method We slightly close a Kocher forceps on a pinch of skin to produce blanching of the skin and then pierce it with a needle to allow a few drops of serum to escape These are placed between a slide and cover glass and examined Our results have not been as favor able as those obtained by MacFie and Corson s technic

In Africa onchocerciasis prevails in Sierra Leone Liberia and the Gold Coast Dahomey, northern part of Nigeria the Cameroons and Congo also reaching Uganda (Strong et al 1934) Onchocerciasis is more extensive in Africa than in America

Robles (1919) has reported onchocerciasis distributed in a zone extending from the fire volcano to the volcano Atitlán at an altitude of 600 and 1200 meters Fulleborn (1932) reported onchocerciasis in Mexico at altitudes between 700 and 1200 meters and Lorenzana (1941) mentions onchocerciasis at 150 to 1700 meters above sea level

ENVIRONMENT

Environment exerts a powerful influence upon the prevalence and spread of the disease In America onchocerciasis is endemic in the coffee plantations this is due to the fact that the workmen are exposed to the bite of the fly which transmits the disease In these temperate hot zones flowing streams are favorable for breeding of the Simulium and workmen who spend the daytime hours in coffee plantations are exposed to attacks of the flies

In Africa in the Province of Lusambo the production of cotton and manioc and the collection of the piassava palm are factors which predispose to infection as are the frequent bathing in streams and the collection of drinking water from such streams (Strong 1938)

MODE OF PROPAGATION

Mexican physicians who are waging a campaign against this disease especially in Chiapas have shown that the disease is spreading They explain this fact by the nomadism of the workmen Frequently workmen who collect the coffee are infected after they come to the plantations then at the end of the harvest they return to their own towns sometimes a considerable distance away thus helping in the dissemination of the disease

The natives of certain localities make long trips to fulfill religious obligations and either pass through or stop in the infested regions When they return home propitious biologic conditions in the environment cause the disease to form a new focus

Infection in Central America and in Mexico is acquired mostly between the months of October and February the dry season During the rainy season the Simulidae almost disappear It is during these months that the coffee crops are being gathered

LABORATORY FINDINGS

The most important laboratory *findings from the standpoint of diagnosis* are (1) microfilariae in the skin or in the conjunctiva (2) microfilariae in the suspected onchocercoma (3) histopathologic findings in the onchocercoma and (4) marked eosinophilia in the peripheral blood

Microfilariae in the Skin and Conjunctiva*—MacFie and Corson s technic consists in taking a piece of skin shaking it in a few drops of saline solution and covering it with a cover glass Microscopic examination should

*See also Chapter 72

TREATMENT

A filaricide has been eagerly sought a product which when injected ingested or applied in some manner might destroy the microfilariae *in the body* of the patient with onchocerciasis Several diluted solutions of neutral red have been used in vitro or in vivo Hoffmann and Vargas (1931) used Plasmochin and Septisemina These authors as well as Estevez (1935) used Atabrine Torroella applied *subconjunctival injection of Plasmochin* for ocular disturbances and Zuniga Cisneros (cited by Hoffmann and Vargas) used it for cutaneous onchocercal lesions This product has been used by Diaz and Giaquinto Mira Some other substances have been tried at the *Medical Center of Huixtla* such as cyanide of mercury Wright used Fuadin Balanzario Rosas (1937) used essential oil of chenopodium Bustamante (1940) calcium gluconate and other chemical substances Unfortunately none proved to be effective

Mazzotti and Hewitt (1948) have used the known filaricide the chloride of 1 diethylcarbamil 4 methylpiperazine (Hetrazan*) on several patients with onchocerciasis They have given 2 mg per kilogram of body weight by mouth for periods varying from 15 to 21 days The results have been good Later trials point to Hetrazan as an efficacious drug against the *Onchocerca volvulus*

Surgical removal of the onchocercoma is the only treatment that improves the cutaneous lesions and prevents ocular invasion sometimes eye disturbances are practically cured (2 cases reported by Pacheco Luna 1942)

PROPHYLAXIS

Two preventive measures should be used first destruction of the vectors and *second* protection *against the bites of the Simulium*

DDT has given the best results in destruction of the vectors not especially adults but the immature form These are the results obtained from experiments in Guatemala and Mexico Blocks of plaster impregnated with DDT were placed in little streams *It has been shown that DDT in water* solution at 1 10 000 000 killed the larvae

With a special apparatus which rhythmically drops a small quantity of DDT similar effects can be secured This should be done in the dry season which in Central America is from October to May Streams are often dry transportation is easier and less expenditure for drugs is needed as well as fewer personnel

In this manner if the Simulidae do not completely disappear at least there is a considerable reduction in the number per area and the inhabitants are bitten much less by the flies Probabilities of being infected are less because the rate of infestation of the flies is low and transmission is particularly difficult

Garnham (1948) described effective measures for killing the Simulium which he carried out in Kenya Africa during the last few years In his com

*Lederle Laboratories Inc

munication he emphasizes that the Simulium never goes into houses and its breeding places are in the tropical forests where it breeds on the rocks under the cascades and waterfalls of rivers flowing through these forests The larva is described as crawling about on rocks under water and eventually becoming fixed as a pupa on a rock right underneath a big waterfall The adult breaks through the pupa s skin and goes up to the surface of the water and flies off He emphasizes that they breed nowhere else except in these places and it was for that reason that an insecticide DDT was placed where they thought it would work best By introducing the insecticide into the river above the area of infestation the poison could eventually come into contact with all Simulium larvae downstream They found that the larvae would then be killed even at a distance of as far as 15 miles A DDT emulsion was placed where there was a water mill into the chute of which the insecticide was allowed to drip The emulsion remained permanent for weeks providing there was thorough mixing It was introduced just over the millrace and then there were dozens of waterfalls downstream ready to re emulsify any of the oil which had separated out River water was added to the emulsion in a 4 gallon tin and the mixture transferred to a similar tin suspended by ropes over the aqueduct of the mill One or 2 holes were made in the bottom of this tin to give a standard rate of delivery For instance a circular hole $^3/_8$ of an inch in diameter dripped approximately 12 gallons in 30 minutes The rate of dosage was 5 parts of DDT in 1 000 000 parts of water This is well above the lethal dose The rate of flow of the water was estimated by the cusecs or the number of cubic feet per second of water DDT was applied every 10 days or fortnight for 5 months and then stopped entirely Garnham s results were sensational He completely eradicated the fly from the area treated The flies began to disappear 2 or 3 weeks after the first dose and the last fly was seen 63 days later They even offered to pay for any fly brought to the station but none was brought The area in which this work was done was about 65 square miles in extent close to a mining region In this area native population surveys showed that at least 86 per cent of the men and 37 per cent of the children were infected Cases already infected remained so but he estimated that there would be no more new cases

Other preventive measures are more difficult to use and less effective nevertheless other measures are advised such as the application of insect re pellent liquids on the unprotected parts of the body Indalone dimethyl phthalate and Rutgers 612 and the formula 622 ' which is a mixture of all three All are harmless To prevent attack by the flies the inhabitants should stay out of the woods streams and places with dense Simulium popula tion as much as possible

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CHAPTER 41

DRACONTIASIS OR GUINEA WORM DISEASE

ALFRED E A HUDSON

DEFINITION

Dracontiasis is the invasion of the tissues of man by a nematode worm *Dracunculus medinensis*

HISTORICAL REVIEW

The worm *Dracunculus medinensis* has been known to man probably longer than any other parasite It has been called by many names the Medina or guinea worm the serpent or dragon worm Velsch in 16 4 referred to it as *Filaria medina* Linnaeus in 1758 as *Filaria medinensis* Several writers (Strong 1945) are of the opinion that this is the fiery serpent that caused the Israelites so much trouble during their stay on the shores of the Red Sea (Numbers 31 referred to by Moses It has also been suggested that it was Moses who taught the sorely oppressed Israelites how to extract the worm by winding it on a small stick

There is no definite proof nor reason to believe that *D medinensis* was the fiery serpent that troubled the Israelites The worm enters the human body in drinking water containing the infected intermediate host the Cyclops The incubation period is 10 to 14 months in the human being Inasmuch as the Israelites complained about lack of water it seems unlikely that this worm was the fiery serpent referred to especially when so very many were bitten or troubled by the serpents spoken of in the Bible

The writings of Agatharchides 140 B C (Strong 1945 contain mention of the worm *Drakontion* Plutarch Galen and Leonides referred to this condition and Paulus Aegineta and Avicenna not only described the symptoms and invasion but they also described the method of extracting the worm Pigafetta (1 98 in his account of his journey through the Congo mentions his observations of infection with this parasite

GEOGRAPHIC DISTRIBUTION

Africa in ancient days as well stocked with this infection to this day there are highly endemic areas in a number of its tropical regions the Nile valley Arabia (the interior and along the Red Sea coast Uganda Equatorial Africa all the way from Mauritania to Gabon Persia Turkestan India especially the west coast around Bombay the Central Provinces patches of the Northwest Provinces and certain areas of Madras chiefly the west of Madura are endemic centers In the eastern half of India the worm is very rare (Chopra 1936)

Strong (1945 states that distribution in indigenous areas is very patchy In India the incidence per 100 000 varies from 6 in Bengal to 3 964 in Mysore and West Madras (Lane and Low in Strong 1945) In Colaba district of Bombay (Pradham 1930) it was found that 10 per cent of the population suffers annually with this parasite while in Deccan at certain seasons nearly one half of the population is bothered with the worm According to Manson Bahr (1944 there are places on the west coast of Africa where nearly every native has one or more of the worms in his body In the southwest part of the Nizam s dominions at Sholapur lives some 15 000 people 95 per cent of whom are acting as host to the *D medinensis* Mirza 193)

Infection has visited the Caribbean the Guianas and a small area of south Brazil It was formerly believed to have been endemic in Fiji Curaçao Demerara and Surinam have

in the past been endemic regions. Chitwood (1933) *found reports of 10 cases of invasion by D medinensis* in human beings in the United States, 4 of whom were of foreign origin There was some doubt as to whether the cause of the infection in the remaining 6 was in reality *D medinensis*, since it was shown by Chitwood (1933) that a species of Dracunculus morphologically *identical with D medinensis occurs in the fox*, raccoon (Chandler, 1942), and mink, in Iowa, Nebraska, New York, and Pennsylvania, and in Ontario, Canada This could possibly have been the guinea worm.

D medinensis has also been found in the fox in the United States by Benbrook (Strong 1945) This parasite has been found as a natural infection in dogs, horses, cattle, polecats, leopards, wolves, gibbons, and baboons from the Old World It is highly improbable that here in the United States man will become infected since the means of transmitting the parasite are lacking and our public health standards as now existing are a distinct barrier to completion of the life cycle by this parasite

ETIOLOGY

The Parasite—*Dracunculus Medinensis* (Linnaeus 1758)

Synonyms—*Gordius medinensis*, Linnaeus, 1758, *Vena medinensis* (Linnaeus 1758) Gallandant, 1773, *Dracunculus graecorum*, Gruner, 1777, *Filaria medinensis* (Linnaeus 1758), Gmelin, 1790, *Furia venamedinensis* (Linnaeus 1758) Modeer 1795, *Fuelleborniius medinensis* (Linnaeus, 1758) Leiper, 1926

Dracunculus medinensis is classified in the subfamily Dracunculineae (Stiles, 1907), family Dracunculidae Leiper, 1912 The females of this family are 35 to 50 times larger than the males *Members of the genus Dracunculus have a cephalic shield, the vulva is near* the head The adult female worms are elongated, cylindrical, and whitish or milky in color At the anterior extremity the worm is bluntly rounded, at the posterior extremity it is recurved Many believe that this formation enables the parasite to retain its hold in tissue *The cuticula is* smooth and unmarked

The mouth is minute, triangular in shape, and lies in an oval or quadrate prominence surrounded by an inner and an outer circle containing papillae The mouth opens directly into the narrow esophagus, merging with the glandular esophagus just in front of the cervical papillae, which Manson Bahr refers to as a single bulb esophagus The glandular esophagus is continued into the cylindrical mid intestine, which empties by a short conical rectal opening consisting of a very minute orifice The uterus seems to occupy nearly the entire body of the mature female, and is densely packed with coiled embryos The vagina apparently becomes obliterated in the mature worm after impregnation The uterine tubes (Looss cited by Strong 1945) open into the posterior part of the esophagus by a common duct, prolapse of the esophagus through the mouth taking place at the time of parturition After delivery of the larvae, it is withdrawn

Leiper (1907) does not hold with the statements above, but believes that the worm discharges its young by prolapse of the uterus, and that this does not take place through the mouth but by rupture just outside the circumoral ring of the papillae, which possibly may represent the vagina

The adult female worm is 75 to 120 cm long by about 1 5 to 1 7 mm wide Napier (1943) and Manson Bahr (1944) gave the size of the female as 32 to 120 cm by 1 5 mm

It is only recently that definite information has been presented concerning the adult male parasites Since the male had not been discovered in man, it was suggested that it disappeared after impregnating the female worm A single male worm, measuring 40 mm, was supposedly found from a natural infection in India In 1906, Leiper, working in Africa, fed a monkey with Cyclops containing infective larvae of *D medinensis* Daniels (1906), 6 months later, found within the monkey 5 immature worms, 2 males and 3 females These worms were placed in the Museum of the London School of Tropical Medicine, but no description has so far been published

Fairley (1925) experimentally fed 22 monkeys *(Macacus sinicus)* with infected Cyclops, but without success

It has been reported that Brug infected Cyclops with the larvae of the guinea worm, then fed these to a gibbon *(Hylobates leucisus)* and more than a year later the seemingly uninfected gibbon was killed and from it was extracted a full grown female *D medinensis* No males were found

The larvae of *D medinensis* do not circulate in the blood or lymph, but remain in the body of the parent worm, and are discharged only at the time of parturition and when the head of the worm comes in contact with water or when the worm is ruptured during extraction. The life span of the larvae in clear water is 6 days, in muddy water or moist earth 2 to 3 weeks The larvae are filiform flattened, with long slender tails and rounded heads The transverse striations of the cuticle are plainly seen

The larvae have no boring apparatus or other means of penetration of the tissues, so that they are unable to enter the integument of their intermediate host, Cyclops (Strong, 1945) They are 550 to 750 by 17 microns The alimentary canal has a rudimentary anus and a bulbous esophagus There are two glands at the root of the tail. The embryos cannot swim in water, but sink, coil, and release again, moving by a side to side lashing of the tail and a tadpole like movement of the body

TRANSMISSION

There is no insect host involved in the transmission of *D medinensis* to man, in this way the method of infection differs from that of other filariidae As the anterior or head end of the adult female nears the human skin, a papule is formed in the dermis, rapidly becoming a vesicle Shortly afterward, the blister ruptures, if the part comes into contact with water, the head of the parasite is thrust out through the opening in the blister Prolapse of the uterus of the parasite then takes place through the ruptured anterior wall of the mouth, and actively motile, first stage larvae are discharged in series into the water The jerky movements of these embryos attract the Cyclops, as a fly attracts a trout, and the larvae are swallowed by the Cyclops The crustacean may contain as many as 20 larvae, but if more than 4 are present, the larvae seem to die While there is no change in their size while in the intermediate host, 2 or 3 ecdyses take place The tail is absorbed, the larvae become cylindrical, and the posterior extremity trilobed Development requires 4 to 6 weeks When they are 1 mm long, they acquire a simple muscular esophagus

The infected Cyclops is swallowed by man in drinking water containing these copepods The gastric juices of the body dissolve the Cyclops, and the larvae become active and burst out Later these larvae pass through the walls of the stomach and the duodenum and migrate through the tissues, where the developed male and female worms lodge in the subcutaneous connective tissue The female worms are mature in 10 to 14 months and are then ready to give up their young It has been suggested that after the male fertilizes the female, it dies and disappears Craig and Faust (1945) have suggested that the female guinea worm may not even require fertilization to produce viable progeny

The Crustacean Intermediate Host

Class Crustacea, subclass Copepoda, order Eucopepoda, genera Cyclops and Diaptomus (water fleas)

Cyclops—The species of this genus measure about one twelfth of an inch (just visible to the naked eye) They are pear shaped, the broad end being anterior They are armed with bristles, the principal organs of locomotion for the Cyclops This small water flea propels itself in short jerks by rapidly flexing these appendages The alimentary tract is a simple tube which extends from the mouth to the anus A dilated portion of this tube is referred to as the stomach. It is here that the embryos of the *D medinensis* are found At least 12 different species can serve as intermediate hosts for the parasite

The known intermediate hosts of the guinea worm are Cyclops coronatus, C bicuspidatus, C quadricornis C prasinus, C viridis, C serrulatus, C strenuus and *C leuckarti*

Manner in Which D Medinensis Infects the Cyclops

It was Fedshenko s (Turkestan) theory that the embryo of the worm penetrates the Cyclops by piercing the exoskeleton between the segments on the ventral surface Wenyon (Manson Bahr 1944) stated that he had seen this take place in his experiments conducted in the Sudan Leiper however, is of the opinion that such infection of the Cyclops does not take place but that invasion of the Cyclops is by way of the alimentary tract Leiper placed large numbers of the *D medinensis* embryos in water then placed several Cyclops in this same water and 6 hours *later found that many of the Cyclops contained several* embryos in the mid intestine These embryos were very active and in no way appeared to be affected by the digestive fluids of the Cyclops Twenty four to 48 hours after the Cyclops had been placed in the water with the embryos the embryos had left the mid intestine and were seen lying in the body cavity It is interesting to note that no digested embryos were seen in the alimentary tract

Roubaud (1929) stated that infection of the Cyclops is via the alimentary tract Roubaud further stated that the nauplius larva of the Cyclops is as susceptible to the infection as are the adult Cyclops and that as many as 3 or 4 embryos are commonly found in a single Cyclops larva Roubaud (Strong 1945) later stated that the embryos of *D medinensis* show no development in the body cavity of the Cyclops even after 3 months Endemic dracontiasis according to Roubaud depends upon a *very complex equilibrium* of relationship between (1) the time required for the annual development of the female *D medinensis* in man (2) the regular recurrence of the necessary seasonal conditions, and (3) the condition of human existence which favor transmission of Cyclops These 3 factors hence have a definite bearing on the prevention of the disease in man

EPIDEMIOLOGY

Infection in human beings results from ingesting water containing the Cyclops which contain the embryos of the guinea worm The parasite is common in small open wells step down wells, or any open water places where infected persons can walk or wade and which contain the intermediate host the Cyclops As most infections in man produce lesions of the legs and feet dissemination of the larvae is facilitated by the step wells

It is a common custom in India for people performing religious ablutions to rinse out their mouths with water This increases the infection if the water is drawn from step wells All persons ingesting water containing the infected Cyclops are susceptible to guinea worm invasion According to Manson Bahr (1944) 38 per cent of the Cyclops in the step wells in India are infected and the infected Cyclops lie at the bottom of the wells Therefore *more people are infected in the dry season* when the wells are practically empty

Washing clothes in wells containing infected Cyclops contributes to infection The great mass of infections in India occur between the months of February and May It is obvious that one invasion by the guinea worm does not protect from another Multiple invasions are common

Sites of Appearance of the Worm

The adult female tends to travel toward the legs and feet The female worm appears in the extremities in 85 to 90 per cent of cases Manson Bahr (1944) states that in India the worm has been known to occur on *the backs of* water carriers who carry the water skins on their backs The worm has been observed in the penis and scrotum In rare cases it has been found in the

arms chest and in the orbit Claree (Strong 1945) has reported a case in which the guinea worm appeared in the tongue

According to Forbes (Strong 1945) the head of the guinea worm appears in 77 per cent of the cases in the legs 22 per cent in the feet 9 per cent in the arms and hands 4 per cent in the abdominal wall 4 5 per cent in the scrotum, 3 5 per cent in the back and buttocks 1 per cent in the eye, and 1 per cent in the penis

Fairley (1925) reports that in 140 persons infected with the guinea worm (harboring a total of 266 worms) the parasite appeared at the surface of the skin of the leg in 218 persons in the arms in 15 in the back in 11 in the buttocks in 5 and in the scrotum in 4

SYMPTOMS

The period of incubation in man is 10 to 14 months During this time the female worm reaches the adult stage and no symptoms appear during this time Lane and Low (Strong 1945) state that in some cases the worm has caused indefinite pains and aching sensations as well as tingling sensations and a feeling as if a cord were under the skin As a rule however no symptoms occur until a few hours before the gravid female makes her appearance near the surface of the skin The early symptoms consist of a local erythema some times a slight fever and a generalized urticaria with intense itching Nausea vomiting and diarrhea may follow (Fairley 1925) In many cases there are intense dyspnea asthma like symptoms and often giddiness and syncope According to Fairley and Liston (1924) these symptoms are the result of the toxic secretions of the worm which are elaborated by it at the time of parturition and quickly absorbed by the host It has been said that the early symptoms perhaps resemble histamine poisoning The symptoms vary greatly of course depending upon the patient s susceptibility A few hours after the onset of the systemic symptoms the local lesion or lesions appear Sometimes however the lesion appears with the symptoms The lesion commences by the formation of small papules or ofttimes a single papule from the center of which the skin becomes raised and a small vesicle or blister appears This inflamed area increases in size during the next day or two The blister and its margin very slowly become more indurated may cover an area 2 mm to 6 cm in diameter This blister usually ruptures if it is not opened and shows a small erosion and small perforation Often the head of the parasite is seen protruding from this opening If the head is not seen and the opening is sprayed with a stream of cold water (from a sponge or syringe) in a very few seconds a drop of milky fluid often exudes and flows upon the surface Sometimes instead of this milky fluid a small tube the uterus of the worm may be projected through the opening when sprayed with cold water In this function the tissues of the head are often ruptured When the uterus has extended through the opening about 1 inch it fills with an opaque milky material ruptures then deflates the fluid running over the surface of the lesion This material contains vast numbers of the embryos of the *D medinensis* Fresh spraying with cold water after an hour or so will bring about the ejec

tion of more embryos or larvae this continuing from time to time *until the* worm is emptied of all its young The expulsion of the larvae is produced by the contraction of the worm when the skin is chilled by the cold water thereby *forcing* out the uterus in small lengths until it is fully emptied



Fig 287 —Drawing of a blister prior to appearance of worm and guinea worm protruding from blister



Fig 288 —Unusual case—guinea worm protruding from tongue Drawn from a description.

With the rupture of the blister usually all toxic symptoms subside Often the area around the worm becomes very much inflamed and edematous with great pain Cellulitis may result due to secondary bacterial invasion

The greatest danger in these cases of guinea worm infection is septic infection with acute cellulitis at the sites of the parasites Often this may take the form of abscess formation without the worm s having perforated the skin and this is likely to occur when the uterus of the worm is ruptured subcutaneously—the irritating substance producing the inflammation More often however this serious complication results from rupture of the uterus after perforation of the skin has taken place often the result of trying to extract the worm in a rough and careless manner before the uterus has had time to empty and while perhaps the terminal hook is deep down in the tissues Staphylococci or streptococci ever present upon the skin now gain entry into the already inflamed tissues and a severe often fatal acute cellulitis is the result

Sometimes the worm dies before reaching maturity or the adult worm fails to come to the surface If there is no associated sepsis it may become absorbed or calcified or an abscess may result In some cases the calcified worms give rise to sciatica synovitis or periostitis Pradhan (1930) states that in India near Bombay in 23 per cent of the cases of guinea worm infection a joint is infected often the ankle which frequently leaves a permanent and crippling condition When the worm is present in the lower part of the leg or foot walking becomes impossible as the foot swells and becomes very inflamed and tender Sometimes the worm invades the breast producing mastitis or a mammary abscess If the worm should invade the scrotum and bacterial invasion take place epididymitis or orchitis might result with ultimate destruction of the testicles

DIAGNOSIS

Diagnosis is often possible only when the worm shows itself at the lesion when ready to discharge its young Often the parasite is clearly outlined just beneath the skin At times the adult worm has been found coiled within an abscess The larvae have been found in fluid aspirated from an affected joint

Exact location of the living worm may be determined by radiography Injections of Lipiodol or Collargol (Hudellet 1919 advised using an injection of 2 c c of 10 per cent Collargol) renders the parasite opaque

The blood picture is not typical although Lane (Strong 1945) found that eosinophilia of 13 per cent was average Many cases however have shown no increase in the eosinophiles

An intradermal test for diagnostic purposes was introduced by Ramsay (1935)

The antigen is obtained by adding 0 25 Gm of the dried guinea worm to 100 c c of ether The mixture is shaken at room temperature for 2 hours to remove the lipoids The dried ether free residue is extracted by shaking for 4 hours in 100 c c of physiolog c saline at 37° C The mixture is centrifuged then passed through a number 6 Seitz filter, and 0 25 c c of this material is used for injection

addition of 5 c c of sterile water produces an emulsion Add another 20 c c of sterile olive oil pour the emulsion into a sterilized 2 oz bottle, seal, and autoclave at 115° C for 30 minutes

"*Injection*

"(1) Assuming the lesion is on the dorsum of the left foot proceed as follows Inject the limb with a 3 per cent solution of Novutox (Novocain) as follows 2 c c *into the vastus medialis* muscle of the left thigh just lateral to its center Make two similar injections, one in the calf muscles in the upper third of the leg and the other in the dorsum of the foot (2) Shake the phenothiazine emulsion vigorously Inject 20 c c *of the emulsion into the vastus* medialis muscle and 10 c c of the remaining 20 c c into each of the other sites into which the Novutox was injected (3) Massage the injection sites firmly for 5 minutes

'It is important to inject half the emulsion as near the buried worm as possible As much as 4 Gm of phenothiazine may be injected at one time if needed

"This preparation should be made and sterilized just before use" (Mackie Hunter and Worth, 1945)

For the treatment of the urticaria and asthma which result from the absorption of the toxins from the parasite the subcutaneous injection of about 10 minims of a 1 1000 solution of adrenalin hydrochloride immediately eases the patient (Fairley and Liston, 1924)

PREVENTION AND CONTROL

Since infection results from drinking water containing Cyclops which *have in their body cavities larvae of D medinensis*, destruction of the Cyclops is important In Africa the ponds in the neighborhood of native villages are sources of infection while in India the step wells are the main source of infection Prevention and control of the disease are dependent upon

1 *Elimination of all step wells* (Leiper, 1907, and Moorthy, 1932)

2 *Destruction of the Cyclops* Treat the water with quicklime in a dilution of 1 1000 (Pradham 1930, and Davis, 1931) When used in a strength of one drachm per gallon, the water is potable in 2 days and is free of copepods for 14 days Copper sulfate plus perchloron is also very effective Caustic potash and permanganate of potash have been used with success in killing the Cyclops in the water None of the above disinfectants will kill the eggs of the Cyclops as effectively as they will kill the adults, with the result that Cyclops reappear in the water within 30 days or so after treatment

3 *Biologic methods of control may be used* The placing of any small plankton feeding minnow will tend to keep down the Cyclops In India in the step wells Moorthy and Sweet (1936) have used *Barbus puckelli* with excellent results These fish were added 1 month after treatment of the water with perchloron

4 For personal prophylaxis *boiling drinking water* will destroy the larvae *Straining the water* through coarse linen will remove the Cyclops The latter method seems the simpler and more practical

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CHAPTER 42

CESTODIASIS OR DISEASES CAUSED BY TAPEWORMS (TAENIASIS, HYDATID DISEASE, HYMENOLEPIASIS, HUMAN DIPYLIDIASIS, HUMAN INERMICAPSIFERIASIS, HUMAN RAILLIETINIASIS, DIPHYLLOBOTHRIASIS SPARGANIASIS)

PEDRO KOURÍ

Platyhelminthes, or flatworms, are metazoa with soft integument, parasitic adult forms without integument, bilaterally symmetrical, no celomic cavity, usually flat more rarely cylindrical (Schistosoma) The majority are hermaphroditic, although some have separate sexes (Schistosoma) They are almost always tape like and segmented (Cestoda), or leaf shaped and not segmented (Trematoda), without digestive tract (Cestoda) or provided with an incomplete digestive tract, without anus (Trematoda), excretory system *bilaterally* symmetrical, ending in flame cells or *solenocytes* The Platyhelminthes generally have organs of attachment such as suckers and hooklets The majority are endoparasites

TAENIASIS SAGINATA AND SOLIUM (BEEF AND PORK TAPEWORM INFECTIONS)

TAENIASIS SAGINATA

(Parasitism Produced by *Taenia Saginata*, the Beef Tapeworm)

Synonyms —Beef tapeworm infection

HISTORY

The common "unarmed" tapeworm of man was observed in ancient times *It was* differentiated from *Taenia solium* by Goeze in 1872 The larval stage was apparently first observed in cattle by Wepfer in 1675 In 1861 Leuckart first demonstrated experimentally that cattle serve as the intermediate host of this worm

GEOGRAPHIC DISTRIBUTION

Taenia saginata is so common in Cuba, and *T solium* so exceptionally rare, that we may regard the former as the only one occurring in that country This scarcity of *T solium* infestation is observed in almost all the countries of the world "except in the Slavic countries, Czechoslovakia and Jugoslavia " (Faust, 1929) Faust states that infection with *T solium* is common wherever raw or inadequately cooked or processed pork is consumed by man The frequency of *T saginata* is probably due to the fact that beef, which is the intermediate host of *T saginata*, is frequently eaten raw or only slightly cooked, as a result the parasites are not destroyed in the preparation of this food Moreover, *Cysticercus bovis* (larval stage *of T saginata) is not as easily detected* in meat as *C cellulosae* (larval stage of

T solium) Infestation with the latter occurs often The pig, a coprophagous animal, can ingest an entire proglottid, and even a fragment of the strobila containing thousands of eggs The larvae localize in the interfascial tissue of the muscles of pigs Since the larvae exist in great numbers, and their color contrasts with that of the muscle fibers, they are easily detectable, and therefore the meat is not eaten On the other hand *C bovis* usually occurs in small numbers because cattle, herbivorous animals, ingest only few eggs, which are found in the adipose tissue and are difficult to detect, so that the contaminated meat is probably eaten

This parasite is found frequently in those countries in which the inhabitants eat raw or slightly cooked beef, as in Ethiopia and Syria In Cuba it is more frequent among Syrians and Spaniards than among the natives, but of course this does not necessarily mean that it is rare among the latter The indigenous people show less infestation with *T saginata*, which is acquired through eating raw beef, than with those other parasites which are acquired through drinking contaminated water or eating vegetables There is more frequent infestation also with those parasites which penetrate through the skin or are inoculated by vector hosts

Kouri and his collaborators in Cuba confirm the above, because beef does not form part of the usual diet of the Cuban rural population Impoverished by a lower economic status, these people are not often able to indulge in the luxury of eating meat When they do they generally eat it well cooked

CAUSATIVE AGENT

Taenia Saginata Goeze, 1782

Synonyms—*Taenia solium* Linnaeus 1763 *pro parte*, *Taenia cucurbitina* Pallas 1781 *pro parte*, *Taenia inermis* Brera 1802, *Taenia dentata* Nicolai 1830, *Taenia lata* Pruner 1847, *Taenia mediocanellata* Kuchenmeister 1852, *Taenia zittavensis* Kuchenmeister 1852, *Taenia abietina* Weinland 1858, *Taeniarhynchus mediocanellatus* Weinland 1858, *Taenia tropica* Moquin Tandon 1860, *Taenia capensis* Moquin Tandon 1860, *Taenia (Cystotaenia) mediocanellata* Leuckart 1863, *Taenia lophosoma* Cobbold 1866, *Taenia nigra* Laboulbene 1875 *Taenia fenestrata* Huber 1896, *Taenia hominis* von Linstow 1902, *Taenia tonkinensis* Railliet and Henry 1905, *Taenia philippina* Garrison 1907

This tapeworm is 4 to 10 meters long Three portions are important the scolex (head), the neck and the body or strobila, which is composed of segments or proglottids

The scolex is at the narrow end of the parasite and resembles a terminal bud when observed with the naked eye it is thicker than the neck The shape of the scolex under the microscope is fusiform with a terminal quadrangular base It has 2 pairs of elliptical suckers 0 7 to 0 8 mm in diameter, which usually contain black pigment It has no rostellum or booklets The neck connects the scolex with the strobila The first segments are short and wide the width is greater than the length They become progressively longer the farther they are from the scolex, although they still remain short and wide for a great portion of the chain They gradually become square, as they reach the end of the chain, the length increases until those at the caudal end (gravid segments) are longer than wide, being 1 to 2 by 0 5 cm Live segments constantly change their shapes by constricting and stretching

An important characteristic of this species is that the gravid segments separate from the strobila and leave the body of the host, either passively in the feces or actively by crossing the anal sphincter and creeping around the perineal and adjacent regions of the host

Bacigalupo's Phenomenon —

As demonstrated by Bacigalupo in 1931, and later proved by Kourí, the gravid proglottid of *T saginata* tears open its terminal uterine ramifications when it separates from the strobila, and thus permits the eggs to escape Korui has observed that expulsion of

Fig 290 —*Taenia saginata* Complete specimen expelled after treatment. *Above* scolex and fine portions of strobila *below* gravid proglottids separated from the strobila. (Original photograph of Kourí)

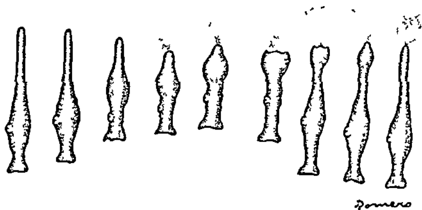


Fig 291 —*Taenia saginata* Different appearances of the same gravid (living) proglottid During contraction a fine white powder composed of thousands of eggs is expelled from one of the extremities (Bacigalupo's phenomenon) (Original drawing of Kourí and Basnuevo in Lecciones de Parasitología y Medicina Tropical courtesy of Editorial Profilaxis S A, Havana)

the eggs takes place at practically every point of the surface c sion possibly occurs also by rupture of the uterine branches at t are being expelled This explains contrary to the accepted conc which eggs are found in the feces by microscopic examination i proglottids have no orifice through which to lay the eggs A simil observed by Kouri and his co workers in the gravid proglottids which expels egg capsules

The *egg* consists of an ovoid embryophore 20 to 30 by 30 to dark brown radially striated wall Inside this embryophore is th onchosphere which is 20 microns in diameter The embryophore is detachable external membrane



Fig 292—*Taenia saginata* Feces covered with gravid proglottids girl (Original photograph of Kouri)

The parasite habitually is anchored to the upper por testine One case has been cited with infestation in the g ing of fragments of the parasite or penetration of gravid appendix is seldom seen yet localization of gravid progl in the appendix is not rare in countries where the parasi Kouri (1927) in Cuba saw *T saginata* infestation of the symptoms of acute appendicitis an emergency operation on this patient Gravid proglottids have been found Fortun, and more recently by Alfonso (1937) In 1940 pendix containing 2 proglottids It had been removed fro

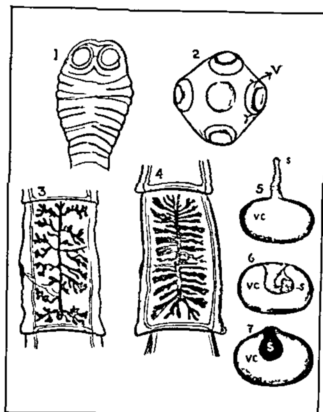


Fig 293 —*Taenia saginata* and *Taenia solium* (modified from Blanchard) *1* and *2* lateral (*1*) and top view (*2*) of the unarmed scolex of *T saginata* V one of the 4 suctorial sulci *3* and *4* gravid segments of *T solium* (*3*) and *T saginata* (*4*) The uterine ramifications are more numerous in *T saginata* (*4*) 5 6 and 7 Cysticercus bovis Protruded scolex in (*5*) and invaginated scolex in (*6*) and (*7*) s scolex vc caudal vesicle

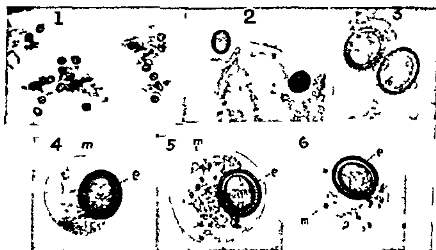


Fig 294 —*Taenia saginata* *1* to *6* Photomicrographs of eggs progressively increasing magnification *4* *5* and *6* *m* external membrane of the egg *e* embryophore containing onchosphere or 6 hooked embryo (Originals of Kouri)



F g 295 —*Taen a sag na a* p otom crograpl s gra id segn ents in the lumen c append x (Ko ri) *1* Histo ogic sect on of an append x w th a cross section of the prog ott ds of *T sag nata* Th s app n l x conta n l 6 proglotti ls pa red and extend the base of the organ w th the long ax s pa al el to the long ax s of the lun en 6 *2* Ma port on of the proglottid with c cut cular zone m n uscu ar zone and u central uterin *3* Per phe al or cut cu ar zone of the proglotti l with c the cut cle s subcuticular cel and c adjacent stroma *4* Stron a of p oglott i sho ing ob que an l c rcu ar musc e fib (below to the left) and the sma l bund es of long musc e fibers cut in cross sect on (a the right) *5* Uter ne ca ty an l eggs 6 Sc emat c dra ing of the append x with prog ott ds p

Usually only 1 parasite is harbored by the host, very seldom 2 to 4 The expression "solitary worm,"* commonly used, is derived from this fact One patient, however, expelled 12 scolices, at least 12 parasites, with about 60 meters of strobila (Kourí)

The host apparently acquires immunity after infestation with the first, or the first few, parasites, which protects him from further infestation with the same species *This may be true during the time he harbors the parasites* If it is true, those cases in which the host harbors more than one parasite can be explained as simultaneous infestations, occurring from a single ingestion of food containing the parasites However, it rarely happens that 12 *Cysticercus bovis* are ingested in a single meal, since beef is not heavily infested as a rule

The life span of the parasite may possibly be several years, although it is usually 2 to 4 years It is necessary, however, to investigate those patients who have been expelling proglottids in their feces for 10 or even 20 years to determine whether these are or are not true reinfestations If immunity exists, reinfestation cannot take place until all parasites have disappeared from the intestines The expulsion of prolottids in the feces will cease for a time until *the new specimens have reached the gravid stage*

Life Cycle

Cattle ingest the embryophores with water or food, the delicate membrane covering these embryophores is dissolved by the gastrointestinal secretions This liberates the hexacanth embryo or onchosphere Although the embryo is ordinarily 20 microns in diameter, it can stretch and become thinner, enabling it to pass through structures They traverse the intestinal mucosa and enter either the portal system or the lymph circulation Thence they are carried to the right side of the heart which sends them through the pulmonary circulation to the left heart From the left ventricle they go through the aorta to all parts of the body localizing in the adipose tissue and in the striated muscles, especially in the cardiac and internal masseter muscles Here they grow and become hydropic Each embryo is finally transformed into a vesicle containing a transparent liquid and an unarmed scolex *This vesicle is the larval form, Cysticercus bovis, which is capable* of infesting man

When raw or slightly cooked beef containing the larvae is eaten, the larval forms (*C bovis*) reach the human intestine The intestinal secretions digest the wall of the cyst, liberating the scolex The scolex anchors itself to the mucosa, the neck proliferates to form the proglottids and develop into the adult worm The formation of the adult tapeworm takes from 2 to 3 months At the end of this period the expulsion of gravid segments begins and hence dissemination of the eggs If these eggs are then ingested by a bovine, a new cycle begins

Cysticercus Bovis

Cysticercus is an ovoid vesicle measuring 5 to 10 by 3 to 4 mm When observed in muscle tissue, it is surrounded by a fibrous capsule If pressed between the fingers, it offers an elastic resistance If this fibrous capsule is opened and dissected, separating it from the cysticercus, the latter appears as an elongated vesicle, thin walled, colorless, and transparent in fresh preparations, but whitish when fixed in 10 per cent formalin. It contains a colorless liquid and an opaque yellowish white body, variable in size, which adheres to the wall, making a prominence in the cavity of the cyst This opaque body corresponds to the invaginated scolex. The larva will die at a temperature of 46° C It

* According to Leuckart the term solium is derived from a Syrian word shushl which is derived from the Arabic word susl or sols It has been Latinized and became the word *sollum* *It has no relationship* to the Latin word solus which means alone or one (Editor's note—R B H G)

will live for a period of about 40 days in meat kept at a temperature of 1° to 4° C It does not survive a temperature of -8° to -10° C for more than 3 hours Its vitality can be determined by adding bile, the presence of bile causes evagination of the scolex if the larva is still alive, or it may produce a whipping motion of the vibratory flame cells in the living cysticercus

Parasitism by this larva is known as *bovine cysticercosis* and is observed in various bovine species and antelopes, seldom in man

Differences Between Taenia Saginata and Taenia Solium

The scolex of *T saginata* is quadrangular and unarmed, while that of *T solium* is spherical and smaller and bears a rostellum with 2 crowns of booklets The uterus of the gravid proglottids of *T saginata* has a greater number of ramifications (15 to 30 each) which are thin and dichotomous, while the uterus of the gravid proglottids of *T solium* has a smaller number of ramifications (5 to 10 each) which are thicker and usually dendritic The gravid proglottids of the former escape one by one either passively in the feces or actively by forcing their way through the anal sphincter The gravid proglottids of the latter are expelled passively in fragments in the feces

T saginata is usually longer and contains a greater number of segments Near the end of the vagina is a sphincter (R de Noyer) *T solium* is shorter, has a smaller number of segments, and the vagina is not provided with a sphincter The larva of *T saginata* *Cysticercus bovis* localizes in adipose tissue and striated muscles It is detected with difficulty because there are few larvae, and their color resembles that of the tissues in which they are embedded The larva of *T solium—C cellulosae*—localizes in the muscle tissue of the pig, and accidentally in man Infestation of pork by these larvae is easy to detect because of the great numbers of parasites and their localization in the interfascial spaces where they offer marked contrast to the tissues which accounts for the rarity of infestation of human beings by *T solium*

PATHOGENICITY

The presence of the adult form of *T saginata* may result in a group of symptoms which when combined are called *taeniasis* The larvae cause *cysticercosis* Cysticercosis is more frequently caused by *C cellulosae* the larval form of *T solium*

SYMPTOMS

The parasite is quite well tolerated by certain individuals, clinical symptoms being totally absent or very mild In nervous people and children this parasite may cause variable symptoms which at times may be very serious

Gastrointestinal disorders may be characterized by an increased appetite (bulimia) or the contrary, total loss of appetite (anorexia) Pressure or pain in the epigastrium, diffuse pain, intestinal colic, and even symptoms similar to those of acute appendicitis are quite frequent Dyspepsia of various types heartburn, eructation, nausea, vomiting, and diarrhea, sometimes alternating with constipation are other common symptoms of this type of parasitosis At times a dysenteriform syndrome has been reported

Appendiceal colic may be caused by 2 different processes (1) penetration of the gravid proglottids into the lumen of the appendix, and (2) friction produced by the passage of the parasite through the ileocecal valve At times the patient expels fragments of the living parasite, this expulsion is accompanied by deep abdominal pains (Brumpt)

Certain nervous reflexes of intestinal origin characterized by weakness dizziness anxiety etc either diminish or totally disappear upon ingestion of food

Hepatic colic accompanied by jaundice and vomiting and even clinical pictures resembling those of hepatic cirrhosis (epistaxis ascites edema etc) have been pointed out in teniasis

Nervous symptoms are often serious especially in children They consist of epileptiform eclamptiform and hysteriform attacks and choreoid phenomena Convulsions accompanied by violent headaches (migraine) and constipation may simulate meningitis (verminous meningismus)

Psychoneurosis is quite common especially in the form of hypochondria or melancholia Kouri observed a case of so called schizophrenia which was cured some time after removal of the tapeworm Cases of catalepsy paralysis strabismus loss of voice dyspnea asphyxia arrhythmia palpitations xanthopsia (yellow vision) diplopia inequality in the pupil (anisocoria) amaurosis and even blindness (periodic or continuous) have been observed Nasal pruritus pruritus ani and urticarial crises have also been seen In some cases the general state of the individual may be affected with loss of weight weakness and mild anemia All these symptoms are undoubtedly of verminous origin since they disappear shortly after expulsion of the parasite

CYSTICERCOSIS

Cysticercosis is frequently caused by the larval form of T solium in man Infestation occurs through ingestion of food contaminated with eggs of the parasite or less frequently in carriers of tapeworms by internal autoinfestation *when the gravid proglottids reach the stomach through violent anti* peristaltic movements The symptoms produced vary in accordance with the location of the cysticercus which in order of frequency are the eye and its adnexa nervous system skin and cellular tissue musculature heart and other viscera When the infestation is intense the cysticercosis may be generalized

Dixon and Hargreaves (1944) have emphasized that cysticercosis is an important cause of convulsions occurring in persons who have been exposed to infestation Their report is based on 10 years of clinical study of 284 cases Autoinfestation seems to be a common occurrence judging from the fact that 26 per cent of the patients gave a history of tapeworm infestation Dixon and Hargreaves emphasize that a tapeworm may be harbored unnoticed for years The symptoms described showed great variety Severe mental deterioration is unusual but changes in personality and disorders of behavior may occur with or without convulsions The diagnosis is not always easy There may be no detectable cysts and no calcification demonstrable radiographically History is of great importance In these cases 274 were undoubtedly infested in the Indian Army It is noteworthy that 2 of their patients had never been outside the British Isles Only 9 were women Nine

were children when infested They believe that a patient with service in India and a suggestive history should be given the benefit of the doubt in spite of repeatedly negative clinical and radiographic investigations

In regard to the curative value of neurosurgery these authors stressed that although the cerebral symptoms may be purely local in character there are as a rule multiple cysts in the brain In none of their cases where the cysticerci were removed from the brain were convulsions relieved The only indication for surgery is threatening blindness from papilledema which calls for decompression They believe that calcified cerebral cysticerci are not unusual and insist that more would be detected if more thorough examinations were made

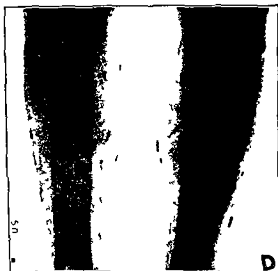


Fig 296 —X ray of the lower limbs of a patient with generalized cysticercosis Note the calcified Cysticerci in the soft tissues (Original of Kouri Basnuevo and Sotolongo)

In suspected cases radiographic search of the whole body is indicated beginning with the limbs At times only a single calcified cyst may be found X ray examinations of the skull are very important Calcification in the brain when it occurs appears to affect mainly the scolex Most films show this type of calcification Radiographs of the skull show that quite frequently a calcified cyst will appears as a shell or halo outside the scolex and occasionally calcification can be seen starting in the cyst wall first

Eosinophilia is not very important since it is found in only approximately 10 per cent of the cases Negative results in complement fixation and skin reactions are valueless as has been found frequently in very heavily infested patients and these tests are not recommended

Incubation period from infestation of body to onset of cerebral symptoms has been found to be from a few months to about 20 years

DIAGNOSIS

Direct Methods

Refer to Chapter 72

Indirect Methods

Eosinophilia is frequent though not constant or specific in parasitism by *T saginata* Complement fixation and intradermal reactions applicable in echinococcosis and other parasitoses have not given satisfactory results in parasitism by *T saginata* It is never necessary to apply these methods in teniasis

TREATMENT

The day before administration of the drugs put the patient on a liquid diet or simply substitute his regular supper with liquid food Instruct him to take a laxative or an enema before going to bed Next day administer the drug then a strong cathartic The patient should have complete rest to prevent nausea and vomiting and should be given a diet of fruit juices

The drugs most frequently used are root bark of the pomegranate tree pelletierine male ferm *(Dryopteris filix mas)* Finland fern pumpkin seeds Kamala thymol chloroform and carbon tetrachloride

The anthelminthic preparation recommended by Kouri and many other physicians is a mixture of an ether extract of *D filix mas* and chemically pure carbon tetrachloride dissolved in enough castor oil to have cathartic effect or in soft gelatinous capsules observing the recommendations above for preparation of the patient

This drug is a taenifuge With it Kouri has obtained 90 to 100 per cent cure (Kouri Basnuevo Sotolongo Nogueira) Due to its prompt purgative action the parasite is expelled in blocks or pellets either complete or at times fragmented or even disintegrated so that it is not necessary that the patient pass his stools in warm water It also eliminates the disagreeable practice of injecting morphine into the parasite as it hangs from the anus of the patient

Although some authors believe that the combination of oil of male fern and carbon tetrachloride is contraindicated Kouri has had no serious consequences with this combination in the thousands of cases of helminthiasis treated with oily solutions of these 2 substances (Kouri and Basnuevo)

Tenicida Kuba (liquid) is administered in doses of 4 c c for each year of age for children and 60 c c for adults and in capsules 1 for each 2 years of age in children and 12 capsules for adults The male fern used in Kouri s formula is an ether extract for Tenicida Kuba liquid and oleoresin for Tenicida Kuba in capsules

Male fern is given in doses of 0 30 to 0 50 c c for each year of age in children and up to 6 to 8 c c for adults * carbon tetrachloride 0 10 to 0 15 c c for each year of age for children and up to 3 c c for adults

*Editor s note (O F) Many Ame can and British authors prefer smal er doses about one half of these

The same plan is followed in treatment of intestinal parasitism by *T solium, Hymenolepis nana Inermicapsifer cubensis Hymenolepis diminuta, Dipylidium caninum Diphyllobothrium latum*

An investigation must be made to determine if the scolex has been expelled too for if it is not the taenia will develop again in about 2 or 3 months In order to determine if the scolex has been expelled the patient should pass all his stools (feces and anthelminthic compound) in a large jar This jar should be carried to the laboratory and its contents washed through a strainer The residue should be examined in a flat dish against a dark background The fact that the scolex cannot be found does not necessarily mean that it has not been expelled for it may have disintegrated or it may be expelled later For this reason it is not advisable to repeat the treatment until the patient begins to expel segments again

PROPHYLAXIS

General prophylaxis consists in preventing the ingestion of meat contaminated with *C bovis* Health authorities should demand efficient inspection of beef before it is released to the public It should be kept in mind that the parasites are found in great numbers in the internal masseter (musculis pterygoideus internus) and heart muscles of the animal Abattoirs should be equipped with autoclaves and refrigeration At temperatures of 8° to 10° C the larvae will die in about 2 or 3 hours The dissemination of contaminated human feces in places where cattle graze should be prevented and all individuals suffering from this parasitosis should be effectively treated

Individual prophylaxis consists in eating only well cooked beef or in substituting lamb or horse meat for beef in the diet

In Arenas examination of 3 000 bovine animals killed in the Industrial Abattoir of Havana 103 animals were shown to be infested with *C bovis* 3 43 per cent of the animals examined This shows clearly the reason for frequency of *T saginata* in human beings in Cuba

TAENIASIS SOLIUM
(THE PORK TAPEWORM)

GEOGRAPHIC DISTRIBUTION

This tapeworm has a cosmopolitan distribution and is found wherever raw or inadequately cooked pork is eaten While it is rare in the United States England and Canada the infection rate is higher in Mexico and Central and South America It is in the Slavic groups in Europe that the disease is most comonly found In Russia the rate varies from 0 2 to 1 5 per cent

CAUSATIVE AGENT

Taenia Solium* Linnaeus 1758

Synonyms —*Taenia cucurbitina* Pallas 1 66 *T pellucida* Goeze 1782 *T vulgaris* Werner 1782 *T dentata* Batsch 1786 *Halysis solium* Zeder 1803 *Taenia armata humana* Brera 1808, *T tenella* Cobbold

*See footnote on p 944

The adult tapeworm measures *from 2 to 3 meters in length but may become as long as 8 meters or more* The scolex is globular with a diameter of 600 microns to 1 mm , it shows pigmentation The rosellum, which is apical and capable of invaginating itself, *carries 2 crowns of hooklets arranged in alternate rows* They number 22 to 32 They vary in size from 160 to 180 microns, some are smaller, 110 to 140 microns The neck is short Behind this structure are the immature, mature, and gravid proglottids The fully developed proglottid is almost a square and while the gravid proglottids are longer than broad, they do not attain the length of the corresponding proglottids of *T saginata* Mature proglottids of *T solium* generally simulate those of *T saginata* except that the testes in the former number 150 to 200 compared with 300 to 400 in *T saginata* The ovary in *T solium* is trilobed instead of bilobed as in *T saginata* The complete strobila of *T solium* usually shows less than 1,000 distinct proglottids

The *eggs* are expelled with fragments of the chain after expulsion from the patient The egg contains a hexacanth embryo or onchosphere about 20 microns in diameter and armed *with 6 stylets The eggs cannot be distinguished from those of T saginata* They come out of the gravid proglottid either before or after the proglottids have become detached from the strobila Outside of the human body they remain viable for weeks in soil, and when ingested by hogs or man hatch immediately The liberated onchosphere penetrates the intestinal wall and reaches the lymphatic or circulatory system The embryos are distributed throughout the body, usually localizing in the musculature or subcutaneous tissue Within 60 to 70 days they become metamorphosed into infective bladder worms or *Cysticercus cellulosae*, measuring 5 by 8 to 10 mm Cysticerci reach man when he ingests raw or inadequately prepared pork The larvae are digested out of the cysts and become attached to the intestinal wall and grow to maturity in 4 to 12 weeks *T solium* adults are believed to have survived as long as 25 years in the intestine of man

Life Cycle

Man is the definitive host of *T solium*, and the hog is the usual intermediate host Two forms of human infection occur When man serves as the definitive host, the adult tapeworm is present in the intestine This infection is acquired by the ingestion of raw or insufficiently cooked pork containing viable cysticerci In cysticercosis man serves as intermediate host in the larval stages, cysticerci are present in the tissues Human infection results from ingestion and subsequent hatching of viable eggs They enter the alimentary canal *in food or drink contaminated by feces from persons harboring the adult worm* Oral infection may occur when eggs are carried from feces to the mouth on the hands of infected persons Occasionally other animals such as dogs or sheep are infected with cysticerci Taeniasis solium infection with the adult worm *is usually not found among Jews or Mohammedans* since they rarely eat pork, but cysticercosis may occur in these people The infection is maintained in nature by improper disposal of human feces which permits ingestion of the eggs by the normal intermediate host, the hog

PATHOGENICITY AND PATHOLOGY

The mature tapeworm in the intestine seldom causes significant pathologic changes, but a moderate eosinophilia may be present The cysticerci may be lodged in any tissue of the body and are most frequently found in the subcutaneous tissues brain eye, skeletal musculature, heart, liver, lungs, and

reaction

imulation

of fibroblast production *The larvae subsequently become encyst* within a fibrous capsule, or necrosis may occur, followed by caseation and calcification Giant cells may be found around the lesion The cysts vary from 0 5 to 2 or even 3 cm in length

SYMPTOMS

Digestive disturbances hunger pains and diarrhea alternating with constipation are found (See Cysticercosis p 946)

DIAGNOSIS

The differentiation between *T saginata* and *T solium* on the basis of appearance of the eggs has been discussed above It is not possible to differentiate them in this manner It is necessary to differentiate between the mature proglottids pressed between 2 slides and held to the light The uterus may be injected with India ink to facilitate the determination of the number of main lateral uterine branches which vary between 7 and 13 in *T solium*

LABORATORY DIAGNOSIS

Examination of mature proglottids as just indicated is vital The differential blood count is of no assistance due to lack of eosinophilia Skin and precipitin tests are not specific Exact diagnosis depends upon recovery of larvae by excision of the cyst and identification of the species by the presence of 2 rows of hooklets of an equal size on the inverted rostellum Stool examination should be made for the presence of eggs

TREATMENT

Oleoresin of Aspidium is the best drug This drug is contraindicated in very old or very young persons There is no specific treatment for cysticercosis The day before the institution of treatment the patient should omit his evening meal or should take only milk and should take an enema before going to bed On the following morning he takes the anthelminthic drug and a purgative remaining in bed to avoid the nausea and vertigo which are sometimes produced by the treatment After the administration of the taenifuge and the purgative the patient prepares a vessel containing tepid water to receive the stools and to preserve the scolex If the scolex does not leave the intestine it is necessary to repeat the medication 2 or 3 times The taenifuges which are most useful are ethereal extract of male fern with or without calomel in a dose of 6 to 8 Gm for adults and 2 to 3 Gm for children Pelletierine which is an alkaloid of this drug should not be given to children because it produces toxic symptoms The following formula is advised

Sulfate of Pelletierine	0 25	Gm
Extract of cocoa	1	Gm
Distilled water	15	Gm
Orange syrup	25	Gm

One half hour after administration of the teniicide give the patient 40 to 60 Gm of castor oil

PROPHYLAXIS

Rigorous exclusion of pork products which have been insufficiently cooked and destruction of feces by sulfuric acid and of all dejecta from the

carriers of taenia to avoid contamination of new intermediate hosts are recommended The campaign against the use of imperfectly cooked pork is the most efficacious method of preventing infestation in man

HYDATID DISEASE (ECHINOCOCCOSIS)

(Parasitism Produced by the Larval Form of *Echinococcus Granulosus*—the Hydatid Worm)

Synonyms—Echinococciasis, echinococcosis, echinococcus disease

HISTORY

Hippocrates, Aretaeus and Galeno knew the disease clinically Redi (1684), Hartmann (1685), and Tyson (1691) suspected its animal nature Pallas (1766) noted the similarity of human hydatidosis to that of other mammals Goeze (1782) was the first to study the scolex of the larva and to compare it with that of Taenia Hartmann (1695) and Rudolphi (1808) studied the adult form in the intestines of dogs Von Siebold (1852), Haubner, Leuckart, Kuchenmeister, and Nettleship fed the scolices from domestic animals to dogs, which then developed the adult worms in their intestines Later Naunyn (1863), Krabbe and Finsen (1863), and Thomas by feeding the scolices from man to dogs, caused the development of the adult form in the dogs

GEOGRAPHIC DISTRIBUTION

Echinococcus granulosus and its larval form, the hydatid cyst, are found in all continents

In Europe the disease is present in Russia, northern Germany, Bulgaria, Hungary, England, France, and Spain, in Asia, in Arabia, Baikal Lake region, Indo China, in Africa, in Algeria, Tunis, Morocco Egypt, Ethiopia, in North America the disease is very rare, in South America it is found in Argentina, Uruguay, Chile, and in Mexico Many cases are imported into Cuba from other countries It is seen in the southern part of Australia (Victoria) and in Tasmania In certain localities 33 per cent of the cattle and sheep are infested

CAUSATIVE AGENT

The disease is produced by the larval form of *Echinococcus granulosus* In its adult form, *E granulosus* is a habitual parasite of the intestines of canines In its larval form it parasitizes the tissues of man, pigs, sheep, cattle, etc, and constitutes what is known as hydatid cyst

Echinococcus Granulosus (Batsch 1786) Rudolphi 1805

Synonyms—*Hydatigena granulosa* Batsch 1786, *Polycephalus hominis* Zeder 1803, *Polycephalus echinococcus* Zeder 1803, *Echinococcus hominis* (Zeder 1800) Rudolphi 1810, *Acephalocystis granulosa* Laennec 1812, *Echinococcus polymorphus* Diesing 1850, *Taenia echinococcus* (Zeder 1803) von Siebold 1853, *Taenia echinococcus veterinorum* (Rudolphi 1810) Kuchenmeister 1885, *Taenia nana* van Beneden 1858 (nec von Siebold 1852), *Echinococcifer echinococcus* Weinland 1861, *Echinococcus hepatis* Scholler 1862, *Echinococcus multilocularis* Leuckart 1863, *Echinococcus alveolaris* Klemm 1883, *Echinococcus cysticus* Huber 1891

This tapeworm is the smallest of the important cestodes of man It is 3 to 6 mm long The scolex is pyriform, provided with 4 ovoid suckers and has a projecting rostrum with a double crown of 30 to 36 hooklets The neck is short, becoming narrow toward the back The strobila is composed of only 3 to 4 proglottids The first is immature, long and wide,

the second is mature, almost twice as long as wide, and shows well developed genital apparatus, both male and female The third and fourth, if present, become gravid and reach a length of 2 mm. and a width of 0 6 mm The uterus, filled with eggs, twists into a spiral, when it is distended, the walls may burst and free the eggs, before or after the gravid proglottid is passed

The *eggs* number 500 to 800 *in the gravid* proglottid They resemble those of *T saginata* and *T solium*, are 32 to 36 by 21 to 30 microns They contain a hexacanth embryo These eggs in the excreta of the dog are very difficult to differentiate from eggs of some species of Taenia and Multiceps

Description of Larva (Hydatid Cyst) —The hydatid cyst is of variable size which may reach the size of the head of an adult human being It is frequently localized in the liver lung, abdominal cavity pelvis or any other part of the body of the host It is composed of 2 parts (1) a fibrous capsule or adventitious membrane formed by proliferation of the connective tissue of the host which limits and encysts the larva and (2) the larva which is found inside the fibrous capsule

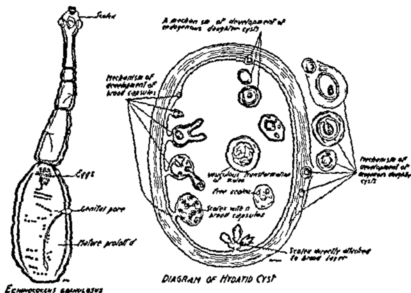
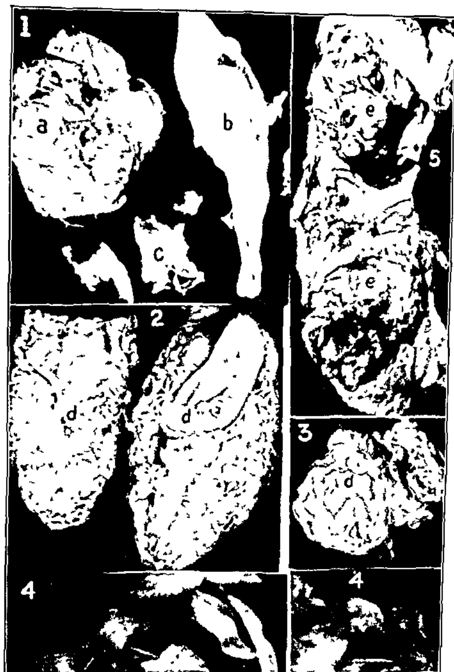


Fig 297 —Schematic drawing of Echinococcus granulosus left adult worm, right larva or hydatid cyst (According to Leuckart in Blanchard and Kouri)

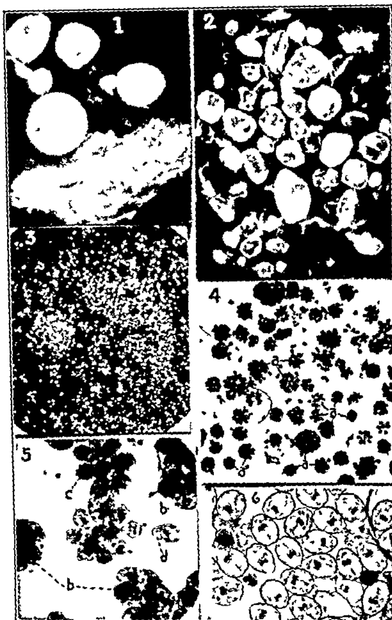
The cyst contains the hydatid liquid which is transparent and colorless In fertile cysts *brood capsules are found in this liquid* and, together with the scolices and loose hooklets, are referred to as hydatid sand Sometimes *endogenous daughter vesicles or cysts* develop from the mother cyst

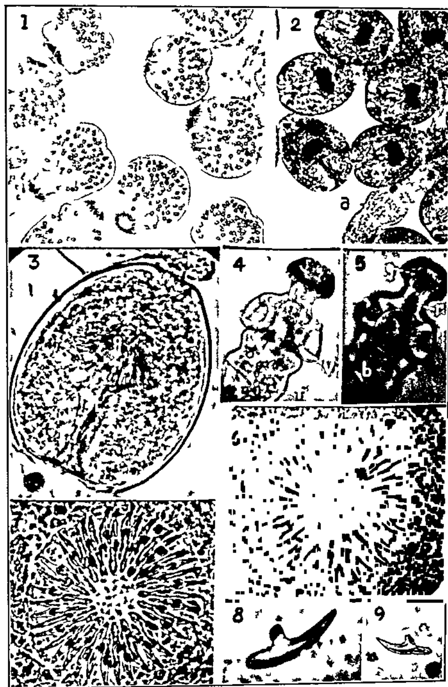
Brood Capsules and Scolex —These capsules are formed by proliferation of the internal germinal layer They are spherical and 0 33 mm in diameter Their walls have the same structure as the germinal layer it gives rise, through internal proliferation to a variable number of scolices These brood capsules, at first attached develop a pedicle and finally are set free in the cystic cavity They form the grains of the hydatid sand

When the brood capsule bursts the scolices become arranged around the membrane which is now in the center Many scolices remain free in the cavity of the cyst They are usually invaginated The crown of hooklets and the 2 pairs of suckers are clearly visible Other scolices are completely or only partially protruded Free hooklets are often found in the cavity of the cyst



...o 5, Five hydatid cysts from the pelvis of a ... years 1, Normal hydatid cyst photograph is no ... olled ... has ... omes ... in ... f the ... and ... ld ... umor ...


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Daughter Cysts or Vesicles—The daughter cysts may be endogenous or exogenous, pendent upon whether they are found inside or outside the true wall of the mother yst They vary in size, sometimes reaching large dimensions The wall has the same ppearance, structure, and functions as that of the mother cyst In the cavity of these daughter cysts there are fluid, brood capsules, and scolices The exogenous daughter cysts develop into new hydatid cysts which are similar to the original cysts Sometimes they communicate with each other and form cysts with an embossed like surface

The daughter cysts may originate in 2 different manners (1) by proliferation (toward the inside or outside) of pieces of the germinal layer confined to the cuticular layer, (2) by vesiculate transformation of the scolices, or by transformation of the brood cap sules The numerous cysts in secondary echinococcosis are developed in the second manner

Hydatid cysts of animals usually lack daughter cysts because animals are usually slaughtered while young, and daughter cysts grow only in cysts which have been de veloping for many years Some hydatid cysts may lack brood capsules and scolices, es pecially in animals, these cysts are known as sterile cysts or acephalocysts These are usually small, young cysts in which the scolices have not had time to develop

Life Cycle

The adult tapeworm is found in great numbers in the intestine of parasitized dogs, its anterior portion imbedded in the mucosa The eggs are expelled in the feces When the eggs are ingested by an intermediate host, they reach the intestine, where their external covering is digested, leaving the embryos free The embryos, aided by their hooklets, bore through the intestinal mucosa and enter the blood capillaries, the lymphatics, and the liver through the portal system Some may remain in the liver or migrate to the right ventricle of the heart and, through the lung circulation, into the left heart They may remain in the lung capillaries or proceed through the aorta and be disseminated to any part of the body A hydatid cyst develops at the point of localization of these embryos The path followed by the embryos in the circulation explains the frequency of the pres ence of hydatid cysts in the liver and the lung

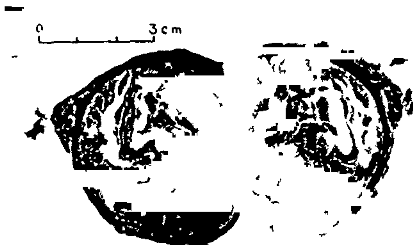
When the definitive host (dog, jackal, wolf) ingests viscera containing a fertile hydatid cyst, the scolices become attached to the intestinal mucosa where they develop into adult parasites The number of adult taeniae which develop in the intestine is proportional to the number of scolices in the ingested cyst A period of 4 to 6 weeks elapses from the time of ingestion to the formation of the adult tapeworm The embryos of *E granulosus* can elongate and pass through the smallest capillaries The development of the embryo in a hydatid cyst is very slow In the first month the larva consists of a nodule 1 mm in diameter containing an embryo approximately 0 33 mm in diameter After the second month the larva has doubled its volume and has become hydropic Th cyst proper is formed after the fifth month Brood vesicles or scolices develop a fe months later

PATHOGENESIS

The development of the hydatid cyst in the host causes the diseases kno as hydatid echinococcosis and alveolar echinococcosis Both diseases vary to the character of the symptoms and lesions produced

Hydatid echinococcosis may be either primary or secondary In former a single hydatid cyst is developed In the latter the rupture of a tile primary hydatid cyst gives rise to multiple secondary cysts The rup may be spontaneous or traumatic, or due to surgical intervention It c a dissemination of numerous scolices into the peritoneum, liver, spleen lungs, with consequent formation of daughter cysts

Hydatıd cyst of the lıver mıght not be notıced When symptoms do appear ıt ıs usuall} several ‹ears after the begınnıng of the dısease At first hepatıc and epıgıstrıc pııns are present which maj or may not radıate to the rıght shoulder Lıck of ıppetıte especıall} for fıts usually accompanıes these



deal solidified hydatid cyst extirpated g 301 was remo ed There were 2 other all of the laughter vesicles, devoid of olid. (Original photograph of Kouri and Tropical courtesy of Ld tor al Profilaxis S A Havana)



Fig 30 —*Ech nococcus gra los s* Photographs of hog's liver filled with hydatid cysts in various stages of development Natural spontaneous infestation (Originals of Aguirre Pequeño)

symptoms If a patıent wıth a hepatıc tumor has a hıstory of relapsıng urtı carıa and a hıgh percentage of eosınophıles ın the blood hydatıdosıs of the lıver ma} be suspected Thıs ıs partıcularly true ıf the patıent comes from a country where thıs parasıtosıs abounds Thıs suspıcıon should be con firmed or excluded b‹ laborator} ın‹ estıgatıons

Later the tumor attains voluminous size and pushes out the abdominal wall causing a noticeable distention of the abdomen The pressure exerted by the tumor may be so great as to cause perforation of the bile ducts and blood vessels

By palpating with one hand and percussing with the other one can feel a hard tumor dull to percussion and frequently painless At times the palpating hand feels the sensation of a definite tremor similar to that produced by touching a mass of gelatin This was pointed out by Briançon and is known as hydatid tremor' It is characteristic of all cysts containing fluid under pressure

Spontaneous recovery may follow death of the larva The cystic fluid is reabsorbed the cuticular membrane becomes folded the tumor becomes solid and may be calcified In such instances it may be well tolerated by the host Spontaneous cure may also follow rupture of the cyst with drainage of its contents into the bile duct intestine and thence elimination in the feces

Death of the larva may be caused by spontaneous bacterial infection or may be subsequent to puncture of the cyst Suppuration accompanied by fever and pain usually follows infection or puncturing of the cyst If the abscess drains to the outside recovery is possible but if it opens into the peritoneum serious complications ensue which may end fatally

Seepage of bile spontaneously or after puncture into the cavity of the cyst kills the parasite but suppuration follows leading to a serious condition

Kouri found in Cuba some cases of hydatid cysts of the liver which were degenerated and filled with a yellow pulp From this yellow mass he isolated fragments of the cuticular membrane These fragments were stained yellow Microscopic examination of the pulp showed characteristic hooklets of the parasite One of these cases was found at operation by Presno in 1927 another by Salas and Lopez on autopsy

In 1937 Vidal and Camejo reported a case of hydatid cyst of the liver spontaneously opening into the bile ducts The patient claimed she expelled little globules in her feces These globules were the daughter vesicles

Cuban medical literature shows numerous cases of hydatid cyst most of them in Spaniards who have been living there for from 10 to 20 years Only one doubtful autochthonous case has been reported

Hydatid cyst of the lung is relatively rare in man It is more frequent among animals Its site is usually the base of the lung more frequently on the right side At first the symptoms may be very slight or absent but after the cyst has attained sufficient size especially if it is superficial the tumor may cause distention of the thoracic wall Vocal fremitus may be diminished or absent The wall of the thorax immediately opposite the infested zone is dull to percussion No vesicular sounds can be heard

Functional symptoms most frequently observed are compression cough dyspnea hemoptysis bronchitis and pleurisy

Spontaneous rupture of the cyst into a bronchus may cause expulsion of a clear salty liquid daughter vesicles and fragments of the cuticular mem

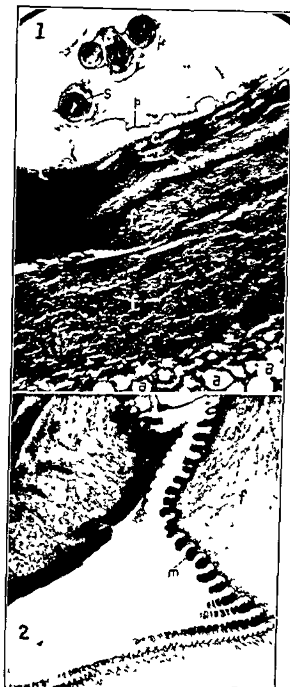


Fig 304 —*Echinococcus granulosus* 1 Photomicrograph of a microscopic section of a hydatid cyst of the lung *S*, scolex *p* germinal membrane *c*, cuticular coat *f*, fibrous capsule *a*, alveoli of the repelled pulmonary parenchyma. 2, Germinal membrane of the wall of a hydatid cyst in the liver of a pig *m* papilla of germinal membrane, *f*, fibrous tissue (Original of Kourí)

brane at times with hemoptysis Scolices and hooklets may be observed microscopically If the cyst bursts into the pleural cavity a hydatid hydropneumothorax is produced

After rupture of the tumor the cavity of the cyst may suppurate and simulate a tuberculous lesion or bronchial dilatation This suppuration may become chronic eventually causing cachexia

Hydatid cysts of the peritoneum are often secondary subsequent to rupture of a primary hydatid cyst Tumors will grow freely in the peritoneal cavity and as a rule attain considerable size They then simulate ascites ovarian cyst or other abdominal tumors

Hydatid cysts of the pelvis are usually secondary These cysts constitute tumors often diagnosed as cysts of the ovary or fibromas They cause symptoms of compression and may be the cause of dystocia

Hydatid cyst of the kidneys is rare As a general rule the infestation consists of a unilateral cyst more often of the left kidney It usually develops in the cortical substance Atrophy of the cortex ensues Compensatory hypertrophy of the healthy kidney develops Signs of renal insufficiency are therefore usually absent

Rupture of the cyst into the renal pelvis occurs more frequently than into the peritoneal and pleural cavities Nephritic colic and mechanical or reflex retention of the urine are commonly present in this case Scolices and hooklets appear in the urine

Hydatid cyst of the brain is not rare It is observed more often in children than in adults The site of infestation may be the meninges the white or the gray substances of the brain The tumor never attains a large size It causes atrophy When the cyst is superficial slow destruction of the cranial bones may occur The symptoms are those of brain tumors It usually causes death

Hydatid cyst of the bones occurs commonly in the pelvis tibia humerus or vertebral column The tumor has a pseudomultilocular aspect It can reabsorb bone tissue

Hydatid cyst of the circulatory system when in the myocardium causes palpitation and arrhythmia Rupture of the cyst into the cardiac cavity produces embolism Similar results follow in cysts of the pulmonary axillary and crural arteries Aneurysm may be produced

Natural Changes in Hydatid Cysts—Cysts may degenerate retract or become calcified Bacterial infection between the cuticular and adventitious membranes kills the larva Bacteria enter the hydatid fluid which being a good culture medium aids their growth abscess formation follows If this abscess drains and opens directly on the outside of the body or into an organ which leads to the outside recovery is possible but if it ruptures into a serous cavity death is almost inevitable

Large cysts have very thin walls and may rupture spontaneously or as a result of mechanical action If the cyst ruptures to the outside of the body recovery may ensue but if it opens into a body cavity the patient might suffer

anaphylactic shock This shock is very seldom fatal Secondary echinococcosis usually develops after dissemination of endogenous daughter cysts brood capsules and scolices into the serosa

DIAGNOSIS

The clinical diagnosis of hydatidosis is very difficult because hydatidosis simulates many diseases depending on the organ in which the larva is found Hydatid cyst should be suspected in an individual who has a hard abdominal tumor with or without hydatid tremors eosinophilia and relapsing urticaria This is especially true if the patient lives or has lived in a country where the parasite is common

X ray pictures showing a distinct circular shadow may be invaluable for the diagnosis especially in cases of pulmonary cysts

Diagnositic puncture should not be performed when the abdominal cavity is the site of infestation The patient is exposed to serious anaphylactic shock by peritoneal absorption of hydatid fluid Bacterial infection of a punctured cyst may cause abscess formation The scolices which escape into the peritoneum may give rise to a secondary echinococcosis

The diagnosis can be established by finding hooklets scolices vesicles membrane or hydatid fluid in feces bile urine sputum or vomica or in the material obtained by puncture operation or at autopsy The finding of hooklets *is important because of their resistance to disintegration even in degen*erating or suppurating cysts

In most cases serologic methods must be used to establish the clinical diagnosis Precipitin complement fixation and intradermal tests may be used*

PROGNOSIS

According to Vegas and Cranwell the death rate in hydatidosis is 13 6 per cent Spontaneous recovery is very rare the prognosis is always grave

TREATMENT

Medical treatment has to date failed to effect cure Tartar emetic and neosalvarsan have been used without success Croste stated that he had obtained good results by using injections of antimony in a relapsing case of hydatidosis This patient had to be operated upon several times When antimony was used the patient recovered

The best treatment is surgical extirpation of the cyst The abdomen is opened and the tumor is sutured to the abdominal wall One per cent formalin is injected marsupialization of the cyst is effected and the parasite is removed

Diagnosis of all cases should be made as early as possible and the operation should be performed immediately after diagnosis

*See Gradwohl and Kourí 1948 pp 529 and 530 and Chapter 7"

PROPHYLAXIS

Theoretically prophylaxis might be effective if the cycle is interrupted at any stage, but practically the easiest thing to do is to keep dogs from becoming infected It is almost impossible to keep man dogs and cattle from contact with each other, but if dogs are prevented from acquiring the parasite, hydatidosis might be reduced in incidence or even completely eliminated

Devé and Blanchard recommend

1 Confiscate and incinerate all contaminated animal viscera

2 Prohibit the presence of dogs in all abattoirs

3 Educate the public about the danger of feeding dogs with viscera from infested animals

4 Insist on proper inspection of all abattoirs by veterinary officials

5 Give fullest publicity to the pathogenesis of echinococcosis and preventive methods

6 Purchase and dispose of all infected viscera (Ivanissevich)

Infested dogs should be destroyed or treated with anthelminthics In Iceland, where dogs are restricted fines have been imposed on those who break the law, this parasitosis has been completely eradicated in that [illegible] In Cuba where echinococcosis has recently appeared it is important [illegible] serious and more thorough inspection of meat in the abattoirs be made Fortunately, veterinarians of the future will be better prepared for this task.

HYMENOLEPIASIS NANA (DWARF TAPEWORM INFECTION)

(Parasitism Produced by *Hymenolepis Nana*)

HISTORY

This species was discovered by Bilharz in 1851 in the small intestine of a [illegible] in Cairo Grassi and Rovelli in 1887 1892 studied the life cycle and [illegible] the parasite does not require an intermediate host

GEOGRAPHIC DISTRIBUTION

H nana is relatively common in certain countries and totally absent [illegible] the same climate and in the same latitude Brumpt believes that this strange [illegible] distribution is due to the fact that the eggs exhibit low resistance to certain [illegible] conditions and die when exposed to them

In Europe it is rarely found in the north quite commonly in the [illegible] has treated numerous cases of adults who had migrated to Cuba from the [illegible] (Asturias) where the parasite is probably very abundant In Africa, the [illegible] in the north (Egypt and Algeria) It has been observed in Transvaal and [illegible] Africa. In Asia it is quite common in Central India where it is found that 10 to [illegible] per cent of the inhabitants are affected (Chandler in the Punjab) It is rare in [illegible], it has been observed in Japan

It is quite rare in New Guinea (0 4 per cent) and the Philippine Islands (1 to 2 per cent), and very rare in Australia It is totally absent in many of the [illegible] East Indian islands

It is frequent in Argentina Uruguay Puerto Rico, and Cuba [illegible] the [illegible] tapeworm in the southern United States It has been observed in [illegible], the Guianas, and other countries

CAUSATIVE AGENT

Hymenolepis Nana (von Siebold 1852) Blanchard, 1891

Synonyms—*Taenia nana* von Siebold 1852 *Taenia aegyptiaca* Bilharz 1852, *Diplacanthus nanus* Weinland 1858 *Hymenolepis fraterna* Stiles 1906

H nana is a small worm 25 to 40 by 0 5 to 0 7 mm The scolex has a retractable rostellum with a single crown of 20 to 30 booklets The neck is long The anterior segments are very short They gradually increase in size although the width is always greater than the length The gravid segments separate from the chain and are partially digested, and then liberate the eggs, which can also free themselves from the gravid segments before the segments separate from the strobila

The *eggs* are spherical or subspherical and have 2 covers *in addition to the wall of the* hexacanth embryo, which can be considered a vitelline embryonic membrane According to Kouri the dimensions are external cover, 47 by 36 microns, internal cover, usually oblong 28 by 23 microns, with a rounded protuberance in each pole, from which rise 4 to 8 sinuous refractive filaments which occupy the space between the 2 covers Within the internal cover is found the onchosphere or hexacanth embryo, 26 by 20 microns The 3 pairs of hooklets are lancet shaped and 11 microns long

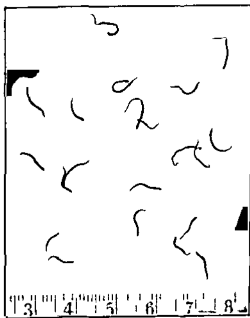


Fig 305—*Hymenolepis nana* Millimeter scale dark background illumination from above Specimens of human origin fixed in 10 per cent formalin (Original photograph of Kouri 1½ times the natural size)

These eggs are colorless and refractive They are usually found in great numbers in direct examination of the feces, due to partial disintegration of the gravid proglottids of the tapeworm, which are very fragile

The parasite is usually found in the distal portions of the ileum of man It is found in certain rodents especially rats and mice In Cuba it is usually found in the gray rat, often associated with *H diminuta* Man acts as both the intermediate and definitive host

Usually massive infestation is seen, especially in children, because of auto infestation Lutz counted up to 2,000 Grassi more than 4 000 Bacigalupo

7 360 Rodriguez Molina more than 7 000 and Kouri 1 000 worms in single cases The parasites are usually expelled in small fragments embedded in mucus

The life span is short in rodents which spontaneously become free of the parasites Older rodents are refractory to infestation This seems to indicate that the animals acquire an immunity The life span in man is impossible to determine because of autoinfestation Parasitism is 3 times more frequent among children than in adults

Life Cycle

H nana has 2 life cycles In the direct life cycle man is both the intermediate and definitive host As the intermediate host he harbors the larval form and as the definitive host the adult parasite In the indirect cycle the larvae develop in fleas *(Ctenocephalides canis Xenopsylla cheopis Pulex irritans Tenebrio molitor* and *T obscurus)*



Fig 306 —*Hymenolepis nana* Two specimens Dark background greatly enlarged fixed in 10 per cent formalin (Original photograph of Kouri)

The *cysticercoid* or larval form of this parasite *(Cercocystis hymenolepis nana)* in the direct cycle has not yet been found in the human intestine but has been studied experimentally

Direct Life Cycle —When the eggs are ingested by the host the hexacanth embryos are set free and attach themselves to the villi of the small intestine After 72 hours the larvae (cercocystis cysticercoid × lex) break through and the scolices become attached to the wall of the intestine Here the neck proliferates resulting in the formation of the adult parasite This process requires eeks Upon reaching gravidity the distal proglottids separate from the parasite disintegrate and liberate the eggs The eggs are expelled in the feces If ingested directly (by external autoinfestation or in contaminated food), they enter the intestine and a new cycle begins

Grassi claims that *H nana* of man and *H fraterna* of rats are the same species, and therefore the life cycle of *H nana in man must be identical with that of H fraterna* in rats According to the studies of Calandruccio, Sacki, Goldman, and Woodland, the life cycle of *H nana* in man is direct, *and identical with that of H fraterna in rats (Brumpt)*

Indirect Life Cycle.—The intermediate host in the indirect cycle is an invertebrate Several authorities found armed cysticercoids in rat fleas *(Ceratophyllus fasciatus, Xenopsylla cheopis) They considered these cysticercoids as the larval forms of H nana* (Dampf, Nicoll and Minchin, Johnston) However, Bacigalupo produced experimental infestation in larvae

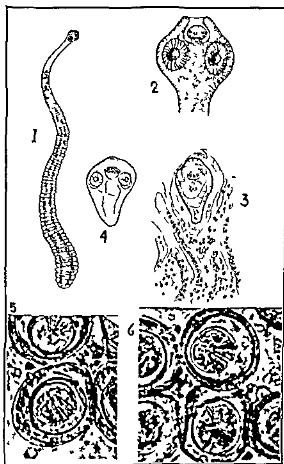


Fig 107—*Hymenolepis nana* 1 Adult ×12 (according to Leuckart) 2 Scolex (according to Blanchard) 3, Cysticercoid of *H fraterna* in an intestinal villus of a mouse (original of Brumpt) 4 Cysticercoid of *H fraterna* recently escaped from a villus to become attached to the intestinal wall of a mouse (original after Brumpt) 5 and 6, Photomicrographs of the eggs of *H nana* in human feces ×600 (originals of Kouri)

of fleas with eggs of *H nana* and *H fraterna* and infested young adults of *T molitor* and *T obscurus* in the same way Later Brumpt succeeded in repeating this experiment with *T molitor* and thus completed the description of the cysticercoid in the body cavity *of these* insects *This type of cysticercoid is different from that developed in the intestinal villi of* the rat

Identification

Do *H nana* and *H fraterna* belong to the same species? This is a very important question from the viewpoint of epidemiology and prophylaxis, since rats may play an *im*

portant role in the propagation of *H nana* in man Differences in the geographic distribution of both parasites as well as differences in location of the parasite in the intestines in experimental infestation of rats have led several authors to consider them 2 distinct species (Joyeux, Blanchard, Bacigalupo)

Bacigalupo claims that when he infested rats with eggs from human feces and with eggs from feces of rats he observed that the former became localized in the distal portions and the latter in the proximal portions of the small intestines of the animals

Kouri noted that, in spontaneous infestation of rats with *H fraterna* large numbers of parasites do not appear, although many parasites are found when man is infested spontaneously Parasites in human feces are much shorter than those obtained from rats, probably due to the fact that specimens obtained after anthelminthic administrations are fragmented Recently Kourí and others confirmed that *H nana* from human sources is much shorter than *H fraterna* from rats

Joyeux tried without success to infest rats with the eggs of Hymenolepis derived from human sources (1920) Later, many other authors succeeded in producing this infestation The percentage of infestation in these experiments however was smaller than that obtained by using eggs from murine sources (Saeki, Uchimura Kiribayashi, Bacigalupo, and Woodland)

It is probable that we are dealing with biologic species or races of the same parasite, as is the case with Ancylostoma of dogs and of cats These 2 species are morphologically identical, nevertheless they are not transmissible from one animal to the other Another example is the Ascaris group The species which infests man does not infest pigs and vice versa These 2 species are however morphologically identical Further investigation in this field is necessary to elucidate this as yet unsolved problem

PATHOGENICITY

Lesions and symptoms are serious because of the intensity of the infestation It causes congestion of the intestinal mucosa, lymphoid infiltrations, and small ulcerations resulting in slight intestinal hemorrhages Frequently clinical pictures of enteritis and nervous symptoms are observed (epileptiform convulsions and laryngospasms) Eosinophilia is usually present

DIAGNOSIS

Diagnosis is established by microscopic examination of the feces for the presence of the eggs which are usually found in large numbers The concentration method of Willis facilitates the discovery of the eggs Direct examination and concentration methods of low and high density solutions should be used (See Chapter 72)

TREATMENT

Treatment is the same as for taeniasis The efficacy of oil of chenopodium has been proved Usually several treatments are necessary, for relapses are quite common Kouri has observed several cases in children over a period of many years These children have been subjected to various treatments with expulsion of numerous parasites without having attained definitive and complete cure

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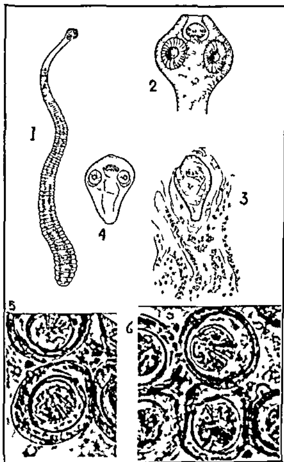


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PROPHYLAXIS

Since both direct infestation by ingestion of the eggs and autoinfestatic are possible, the prophylactic procedure is the same as that followed in enter biasis Parasitized children should be treated and kept from contact wi other children It should be remembered that ingestion of the arthropod intermediate hosts of the parasite constitutes another method of contractir the disease Rats are the habitual host of *H fraterna*, which is considered b some authors to be identical with *H nana* If this is true, then the feces of par sitized rats are sources of infestation Fleas (*Xenopsylla cheopis* and *Cerat phyllus fasciatus*) of these rats are another source of infestation

HYMENOLEPIASIS DIMINUTA (THE RAT TAPEWORM INFECTION

(Parasitism Produced by the Rat Tapeworm)

HISTORY

Hymenolepis diminuta, a common tapeworm of the mouse and rat, is also found in mai It was discovered by Olfers in 1766 in rats in Rio de Janeiro and was described in man b Weinland in 1858

Hymenolepis Diminuta in Man

According to Riley and Shannon 61 cases of human parasitism by *H diminuta* had bee reported up to 1922 Between 1922 and 1944, more than 200 additional cases of huma parasitism with this tapeworm were reported 15 of which occurred in Cuba where it infest white and gray rats Other cases were reported in Argentina, Brazil, Costa Rica, the Unite States Ecuador, Guatemala, Mexico Granada Martinique Nicaragua, Belgium, Italy, Eas Africa, U S S R , Japan, India, and the Philippines

Man is accidentally infected by swallowing insects or other arthropods parasitized by the *larval form* *These insects have previously been infected by ingesting the eggs of the parasite* disseminated in the excreta of the Muridae, their habitual definitive hosts The number of parasites harbored is usually 1 to 3, although cases have been reported with as many as 19 specimens

CAUSATIVE AGENT

Hymenolepis (Hymenolepis) Diminuta (Rudolphi 1819) Blanchard, 1891

Synonyms.—*Taenia diminuta*, Rudolphi 1819, *T leptocephala* Creplin 1825, *T flavo punctata*, Weinland 1858, *T varesina* Paroma 1884, *T minima*, Grassi, 1886, *Hymenolepis diminuta* R Blanchard 1891

The *adult worm* is 20 to 60 cm at times 75 cm long, and about 3 5 mm. wide, and has a small scolex, 200 to 300 microns in diameter, which bears a rudimentary unarmed rostellum without hooklets The rostellum is hidden in a small infundibulum The neck is short, measuring 500 by 150 microns

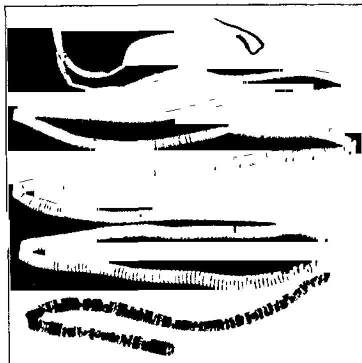
The proglottids, including those which are gravid, are rather short and wide The caudal proglottids become separated from the rest of the strobila, partly distinegrate, and liberate the eggs The eggs frequently leave the gravid proglottids in the last tenth of the strobila before detachment of the proglottids

The *eggs* are spherical and *have 2 walls and a hexacanth embryo* *The outer wall is* yellowish, radially striated and the inner surface wrinkled The diameter is 60 to 80 microns The inner wall is refractive and colorless It encloses the hexacanth embryo 36 microns by 28 The hooklets of the embryo are 11 microns long

Life Cycle

The life cycle is indirect and requires an intermediate host. The eggs are passed in the feces and are ingested by an insect which acts as intermediate host, and embryos are liberated in the digestive tract of the insect. These embryos bore through the wall and localize in the body cavity, where they develop into the larval or cysticercoid form *(Cercocystis hymenolepis diminuta)*.

Joyeux has demonstrated that the larvae of the rat flea *(Ceratophyllus fasciatus* and *Xenopsylla cheopis)* are infested by the embryos. In this case the embryos develop into adult forms before the larvae of the insects attain their adult state. Grassi and Rovelli have demonstrated experimentally that the cysticercoids ingested by rats, mice, or man develop into adult forms in a period of 15 days.



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Intermediate Hosts —

The following are known to be spontaneously infested:

Asopia (Pyralis) farinalis (caterpillar and butterfly), *Akis spinosa*, *Scaurus striatus*, *Dermestes peruvianus* (larva), *Ulosoma parvicornis* (adult stage), *Anisolabis annulipes* (earwig), *Ceratophyllus fasciatus*, and *Xenopsylla cheopis*.

The following have been experimentally infested:

Tinea granella, *T. lionella*, *Aglossa dimidiata*, *Aphomia gularis*, *Tenebrio molitor* (adult stage only), *Geotrupes sylvaticus*, *Leptopsylla musculi*, *Ctenocephalides canis*, *Pulex irritans*, *Ceratophyllus wickami* (larval stage only), *Fontaria virginica*.

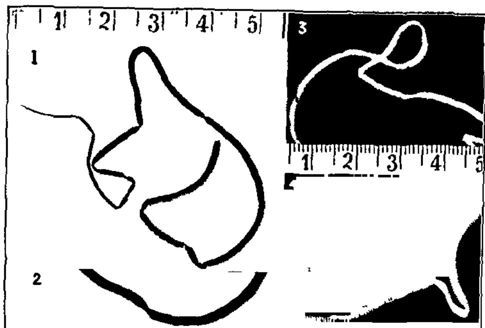


Fig 309 —*Hymenolepis diminuta* Smaller specimen derived from rat *1*, Complete small specimen *2*, *3*, and *4*, Fragments of a larger specimen Note the finely serrated borders and the transverse striations which are very close together and resemble the segments Dark background illumination from above Millimeter scale (×1 80) (Originals of Kouri)

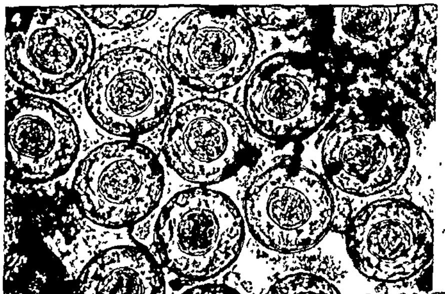


Fig 310 —*Hymenolepis diminuta* eggs (×310) from the gravid proglottids They are large and spherical and have 2 widely separated walls The outer wall is yellow with radial striations, its inner surface wrinkled The inner wall is smooth, colorless and refractive and not so definitely round as the outer wall The inner membrane contains the embryo with 3 pairs of hooklets (Original photomicrographs of Kouri)

According to Joyeux, cockroaches are not infested According to Bacigalupo, the following insects act as intermediate hosts in Argentina *Dermestes vulpinus* Fabricius, *Dermestes peruvianus* Castelnau, *Ulosonia parvicornis* Fairmaire, *Anisolabis annulipes* Lucas, *Embia (Rhagadochir) argentina* Navas

PATHOGENICITY AND SYMPTOMATOLOGY

Pathogenicity and symptomatology are in general similar to the taeniases

DIAGNOSIS

Diagnosis is made by microscopic examination of feces for the presence of the eggs Direct and concentration methods should be used

TREATMENT

Treatment is the same as for taeniases in general, although sometimes the patient expels the complete parasite or part of it, spontaneously or following a purgative

PROPHYLAXIS

Ingestion of insects infested with the larvae of the parasite should be prevented *Asopia farinalis*, a lepidopterid often found in flour, may be ingested by eating bread which is not well baked Rat fleas (*Xenopsylla cheopis* and *Ceratophyllus fasciatus*) and dog fleas (*Ctenocephalides canis*) may contaminate man, especially children

HUMAN DIPYLIDIASIS

(DOG TAPEWORM INFECTION)

(Parasitism Produced by *Dipylidium Caninum*, the Double Pored Dog Tapeworm)

CAUSATIVE AGENT

Dipylidium Caninum (Linnaeus 1758) Railliet 1892

Synonyms —*Taenia canina* Linnaeus 1758 *pro parte*, *T moniliformis* Pallas 1781, *T cucumerina* Bloch 1782, *T elliptica* Goeze 1783, *T cateniformis* Goeze 1782, *Alyselminthus cuneiceps* Zeder 1800, *T canina felis* Rudolphi 1810, *T prismatica* Rudolphi 1810, *T cunipes* Diamare 1893, *Dipylidium cati* Neumann 1896, *D oerleyi* von Ratz 1900, *D sexcoronatum* von Ratz 1900, *D walkeri* Sondhi 1923, *D halli* Tubangui 1925, *D compactum* Millzner 1926, *D crassum* Millzner 1926, *D diffusum* Millzner 1926, *D gracili* Millzner 1926, *D longulum* Millzner 1926, *D caninum* López Neyra 1927, *D carracidoi* López Neyra 1928, *D porimamillanum* López Neyra 1928

This tapeworm is a habitual parasite of the intestines of dogs and cats The parasite was found in large numbers in 50 per cent of dogs autopsied in Havana (Arenas, Kouri, Basnuevo, 1933)

According to Blanchard (1907), 60 cases of human parasitism by *D caninum* had been reported up to 1907 Since that date, new cases have been reported in different countries The number of human cases has been increased by several hundreds in Germany, Denmark Italy Switzerland, Norway, Sweden, Austria, Holland, France, England, United States, Costa Rica Philippines, Japan, and China Fermoselle and Portuondo (1936) reported the first case in Costa Rica. We believe that human parasitism by this worm, especially among children, is not so infrequent as it seems Many cases remain unknown for some time because of the difficulty of establishing the diagnosis.

No human cases had been reported in Cuba until recently Calderín, a student of Kourí, presented a specimen which had been passed by a young girl Some time later, Kourí had the opportunity of studying another case in a human being from the province of Oriente This patient expelled several specimens of this parasite

In 1943, Montero reported another patient from Oriente, Cuba This was a child who had spontaneously expelled 3 specimens In Camaguey, Cuba, one case reported by Rodríguez León was a child who had expelled 5 specimens of the parasite, which were sent to Kourí for confirmation Another case report was sent by Manuel Sáinz Ortiz and Rivacoba, of Moron One case report was sent from the province of Las Villas, Cuba, by Federico Escobar of Ranchuelo, and 2 patients were reported by Iznaga in 1942 Two patients were treated at the Institute of Tropical Medicine of the University of Havana (Kourí, Basnuevo, Sotolongo), making a total of 10 cases of human dipylidiasis reported in Cuba up to 1944

Dipylidium caninum is 10 to 50 cm by 2 to 3 mm The scolex is relatively small, although larger than that of *H nana* and *H diminuta*, and has a retractile rostellum which bears 4 crowns of thorn like hooklets The size of the hooklets decreases gradually from the anterior to the posterior crown which bears the smallest hooklets There are 4 large, elliptical suckers



Fig 311 —*Dipylidium caninum* complete specimen large size in 10 per cent formalin Dark background illuminated from above Millimeter scale (X1 60) (Original photograph of Kourí, Arenas and Basnuevo)

The mature and gravid proglottids are longer than wide They have convex borders and resemble cucumber seeds

The *eggs* are almost spherical, 52 by 45 microns There are 2 thin covers, the inner, 33 by 31 microns, containing a hexacanth embryo, 28 to 30 microns in diameter, with hooklets 9 microns long

The eggs occur in groups of 8 to 16 within the oviferous capsule, which is enclosed within the gravid proglottid

This parasite is found in the upper small intestines of dogs and cats One case of localization in the gall bladder and one of encysted proglottids in the colon of an infected cat are known

The number of parasites harbored is at times considerable, especially in young animals The number in human cases is 1 to 5 specimens

Life Cycle

The gravid proglottids pass outside the body and there expel oviferous capsules containing eggs These eggs are ingested by intermediate hosts, dog lice and fleas *(Trichodectes*

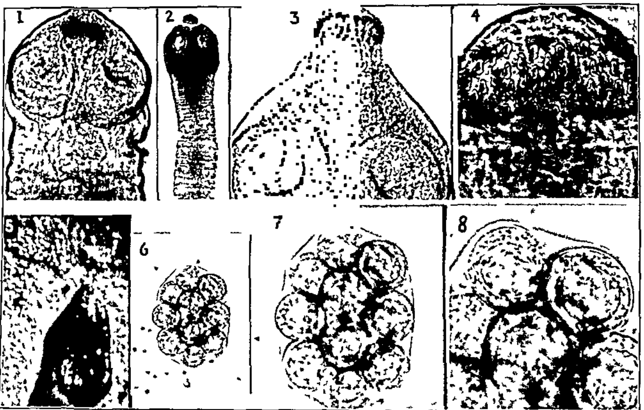


Fig. 317.—*Dipylidium caninum.* 1, Scolex with invaginated rostellum and crown of hooklets. Note 2 of the suckers. 2, Scolex with protruding rostellum and crowns of hooklets. Note neck and suckers. 3, Scolex with rostellum completely protruded and bearing 4 crowns of hooklets. Note 2 of the suckers. 4, Protruded rostellum bearing 4 crowns of thornlike hooklets. The hooklets decrease in size gradually from the upper to the lower crown. 5, Phenomenon of laying oviferous capsules by the gravid living segments liberated from the strobila and passed in the feces (Kouri). Illuminated from above, gray background. The clusters of white lines toward the narrower pole of the gravid segment are oviferous capsules. 6, 7 and 8, Oviferous capsules with different magnifications. They contain a variable number of eggs with double thin wall, colorless and refractive. The egg contains a hexacanth embryo or oncosphere. (Original photomicrographs of Kouri.)

canis and *Ctenocephalides canis*), and the human flea (*Pulex irritans*) They localize in the body cavities of these insects and develop into larvae *Cryptocystis trichodectis* Joyeux has demonstrated that fleas become infested while in the larval state and that the cysticercoid develops when the insect reaches the adult form The definitive host (usually dogs and cats, accidentally man) becomes infested by ingestion of parasitized fleas and lice

DIAGNOSIS

The diagnosis, as a rule, remains unsuspected until the gravid proglottids or fragments of the parasite are accidentally discovered in the feces Since the eggs or oviferous capsules usually do not appear in the feces microscopic examination of the feces is insufficient The therapeutic test might be useful in diagnosis The gravid proglottids of *D caninum*, like those of *T saginata*, are found singly outside the body, therefore, the discovery of these segments is sufficient evidence to establish the diagnosis

Examination of the feces includes microscopic examination, direct and by concentration methods and macroscopic examination, direct and by screening

When the gravid proglottids are received in a dry state, they are contracted and of an amber color They regain their original appearance if placed in water

Another point of similarity between *T saginata* and *D caninum* is an observation made by Kouri of a "phenomenon of laying oviferous capsules" through one of the poles of the gravid proglottid of *D caninum* This phenomenon is similar to that described by Bacigalupo in the gravid segment of *T saginata*

TREATMENT

The treatment is the same as for taeniasis although at times the patients spontaneously expel the parasites

PROPHYLAXIS

Handling of dogs which might be infested is to be avoided as much as possible Fleas and lice from these animals contaminate food Since dogs are domestic animals and it is almost impossible to separate them completely from man, one should try to rid them of this parasite Parasitism in dogs is usually intense because these animals eat their fleas and lice It is advisable to rid dogs of fleas and lice Keep them from living on the ground in dark, wet places where optimal conditions are likely to exist for the development of these insects

HUMAN INERMICAPSIFERIASIS

(Parasitism Produced by *Inermicapsifer Cubensis*)

HISTORY

The first case was reported in 1930 a second case in 1935 2 in 1937, 11 in 1939, 17 more in 1940, making a total of 32 cases reported from 1930 to 1940 There has been a rapid increase in the number of cases reported each year To date more than 75 cases of human parasitism with this tapeworm have been reported in Cuba

GEOGRAPHIC DISTRIBUTION

Inermicapsifer cubensis can probably be found throughout the 6 provinces of Cuba, although most of the cases come from the 4 western provinces The greatest numbers have been reported in the province of Havana, followed, in order, by Las Villas, Matanzas, and Pinar del Rio Forty five cases have been reported from the Province of Havana, where large foci are in Bejucal, Santiago de las Vegas, Rancho Boyeros Cases have been reported in San Antonio de lo Baños, Guira de Melena, Quivicán, La Salud, La Víbora, City of Havana, and Peparto Miramar Some cases were from Marianao, Bauta, and Guanabana

Hernández and Fatralgo, of Santa Clara, province of Las Villas, reported 4 cases in 1943, and Ramos of Caibarién reported 5 Kouri and Basnuevo also reported 1 case from Santa Isabel de las Lajas Twelve cases have been reported from the province of Las Villas to date

In the province of Matanzas, 1 case came from Agramonte, 3 from Cabezas, and 2 from the city of Matanzas Fourteen cases have been reported to date

In the province of Pinar del Rio, 2 cases were from the city of Pinar del Rio and 3 from Artemisa One specimen was submitted to Kouri by I Ortiz from Lara, Venezuela Its existence is suspected in Puerto Rico

CAUSATIVE AGENT

Inermicapsifer Cubensis (Kouri 1938) Kouri 1940

Synonyms —*Raillietina cubensis* Kouri 1938, *Raillietina (R) kouridovali* Dollfus 1940, *Raillietina (R) loechesalavezi* Dollfus 1940

This cestode measures 27 to 42 cm and has 310 to 368 proglottids The scolex, without rostellum or hooklets, is approximately 630 by 610 microns The suckers are unarmed They are about 185 microns in the longest diameter, and about 150 microns deep The neck has been estimated to be 3 mm long Proglottids of the midportion of the strobila are broader than long, about 2 3 by 1 5 mm The gravid proglottids, which are discharged in the feces, are 3 to 3 75 by 1 to 2 mm The free living gravid proglottid has variable shapes, but when fixed in 10 per cent formalin, it tends to become round and is rather opaque If allowed to die before fixation, it becomes elongated, flat, and transparent The gravid proglottids contain 48 to 175 egg capsules, varying greatly in size and shape Each contains 6 to 11 eggs, 55 by 49 microns The shell has 3 layers, within the shell is a small hexacanth embryo, 22 by 19 microns, the hooklets of which are approximately 6 microns long For further details, see Gradwohl and Kouri (1948)

Life Cycle —Unknown

Number and Life Span.—The patients usually harbor a single specimen Two of Kouri s patients expelled 2 specimens each, when treated, another patient expelled 3 A patient of Nogueira expelled 4 specimens after administration of treatment Seven specimens were harbored by a 2 year old child (Kouri and Sotolongo)

The life span of the parasite in its human host does not seem to be very prolonged, *usually several months The parasite is not very resistant within human hosts*, which usually are infants, rarely adults Man is probably an accidental host, the parasite is easily expelled with the administration of castor oil or any other cathartic However, one of Kouri s patients (according to the patient's mother) had expelled gravid proglottids continuously for 6 years

SYMPTOMS

Age —In most of the cases the ages of the patients ranged from 1 to 2 years (18 cases) although there are cases of children less than 1 year old, of

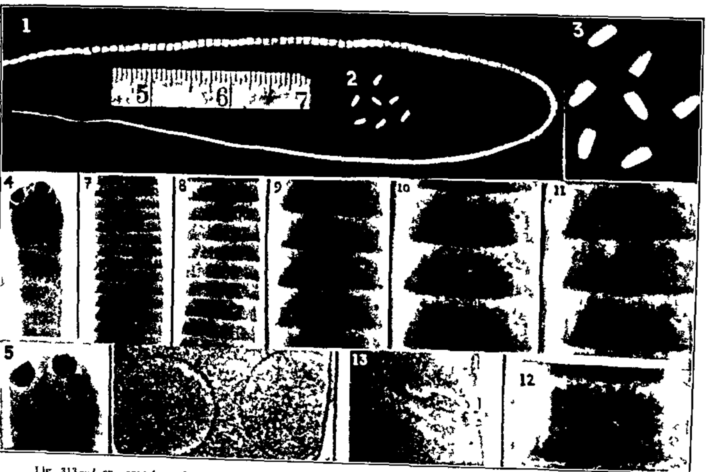


Fig. 313.—*Inermicapsifer cubensis* (Kouri, 1939). *1* to *3* Photographs, dark background, illuminated from above. Specimens fixed in 10 per cent formalin. *1* Entire specimen expelled by a 9 year old boy during treatment. Four fifths natural size; scale in inches. Case treated by Kouri and Macho Doval. *2* Mature proglottids life size, freed from the strobila and expelled in the feces. *3* Same proglottid magnified. *4* to *13* Photomicrographs of various magnifications. Specimen fixed in 10 per cent formalin. Illuminated from below. *4* and *5* Scolex and neck. Two pairs of suckers. *6* Two of the suckers, magnified. *7* to *12* Proglottids from different sections of the strobila. *13* Unilateral genital pores in the center of the edge of the proglottid. Small cirrus bursa. (Originals of Kouri.)

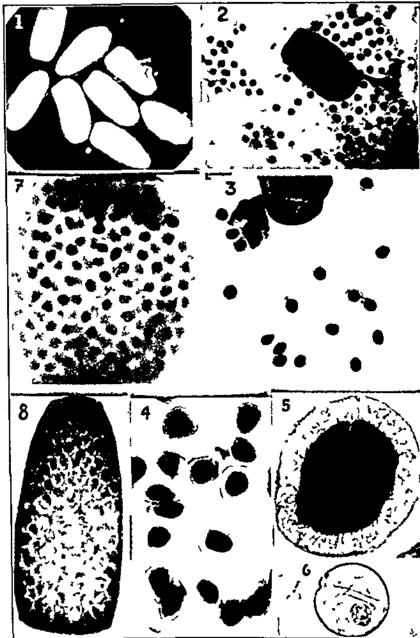


Fig 314 —*Iner caps fer cubens s* (Kouri 1939) *1* Eight mature proglottids. Low magnification specimen fixed in 10 per cent formalin dark backgroun i illuminated from

[illegible]

s etios k u x i i j o (g ai s of Kouri)


1
2
3
4

older children, and even of adults although the Fifty seven patients were children below the age patients 1 was 16 years old 1 was 18 and 1 was 35 were 3 to 4 years old 11 were 2 to 3 years 7 w youngest was 5 months old



Fig 316 *Inermicapsifer cubensis* (Kouri 1939) One o after treatment It is 4 cm long and has 368 proglottids beg the scolex (Original photograph of Kouri and Basnuevo R Medicina Tropical courtesy of Editorial Tropical S A Hav

Sex —Of 62 cases reported 33 or 5 per cent



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older children, and even of adults, although these cases are less frequent. Fifty seven patients were children below the age of 13 years, 3 were older patients, 1 was 16 years old, 1 was 18 and 1 was 35 years of age. Nine patients were 3 to 4 years old, 11 were 2 to 3 years, 7 were 4 to 5 years old. The youngest was 5 months old.



Fig. 316.—*Inermicapsifer cubensis* (Kouri, 1939). One of 3 complete specimens expelled after treatment. It is 42 cm. long and has 368 proglottids, beginning the count 4.52 mm. from the scolex. (Original photograph of Kouri and Basnuevo in Lecciones de Parasitologia y Medicina Tropical, courtesy of Editorial Profilaxis S. A., Havana.)

Sex.—Of 62 cases reported, 33, or 53.5 per cent, were male.

Race.—In all 57 cases where a record of the race was made, patients belonged to the white race with the exception of 2 Negro patients.

The parasite may give rise to mild symptoms in some patients, in others the symptomatology has not been ascertained.

DIAGNOSIS

Usually infestation is discovered by the presence of small whitish objects resembling rice grains in the feces These are often noted by the parents Frequently expulsion of fragments of strobila in the feces either spontaneously or after the administration of cathartics makes the diagnosis possible Microscopic examination of the feces is negative but by macroscopic examination one may recover the gravid proglottids which rise to the surface of the fecal matter several minutes after it has been passed The best procedure for identification of these gravid proglottids and differentiation of them from *starch fragments and rice grains is to compress them between a slide* and cover slip If they are actually gravid proglottids of the parasite they will burst and liberate a great number of characteristic oviferous capsules Dilution and screening of the feces using 3 screens of decreasing mesh should be performed when searching for this parasite

The gravid proglottids when alive slowly change shape due to the slow creeping movements If they are fixed in 10 per cent formalin while still alive they assume a spherical shape and become whiter and more opaque If they die spontaneously they are in muscular relaxation and are then elongated and flattened and more transparent (Kouri)



Fig 317—*Inermicapsifer cubensis* (Kouri 1939) Eggs obtained by crushing egg capsules between slide and cover slip Medium magnification (Original photomicrograph of Kouri and Basnuevo in Lecciones de Parasitologia y Medicina Tropical courtesy of Editorial Profilaxis S A Havana.)

TREATMENT

The parasite is expelled with relative ease Castor oil or any oil cathartic frequently administered to children by their mothers results in the expulsion in some cases of fragments of strobila and even of the entire parasite

Spontaneous expulsion of the entire parasite with scolex and numerous proglottids occasionally takes place Recently a patient to whom we had administered 3 treatments with negative results and who constantly passed proglottids during the intervals between treatments spontaneously expelled an entire parasite and a great number of proglottids while taking *Bacillus acidophilus* as milk treatment for fever and digestive disorders

Kouri et al use and recommend a mixture of an ether extract of male fern (Aspidium) and carbon tetrachloride in an oil suspension (Teniceida Kuba) The dosage is 4 c c per year of age in 1 complete single dose Two to 4 hours later a saline cathartic should be administered

For adults we use a dose of 60 c c

One patient who was given Necato Kuba expelled 2 complete parasites

PROPYHYLAXIS

Although the biology of this parasite is unknown we should take the same general precautions as with other intestinal helminthiases The manner in which man becomes infested with the parasite has not as yet been determined We are not concerned with which is the definitive habitual or normal host or with whether the parasite has a direct or indirect cycle that is if it does or does not need an intermediate host during its life cycle

HUMAN RAILLIETINOSIS

(Parasitism Produced by Species of Raillietina)

Raillietina (R) Quitensis (Leon 1938) Joyeux and Baer 1940

The characteristics as described by Luis A León are as follows This cestode is 10 to 12 meters long and 3 mm wide at the caudal end This estimate is considered somewhat exaggerated (Joyeux and Baer in view of the fact that several worms expelled at the same time might have been considered as a single individual The scolex is 1 by 0 5 mm The rostellum is retractile and has 2 crowns of concentric hammer-shaped hooklets The suckers are ovoid and are about 0 5 mm long They are armed with a row of permanent hooklets Each specimen consists of more than 5,000 segments The anterior segments are wider than long the center segments square and the gravid segments at the caudal end rectangular In the free state these proglottids are ovoid and resemble grains of rice Each terminal proglottid contains 200 to 250 ovifero s capsules which are polygonal 200 microns in diameter The oncospheres are ovoid and are provided with long hooklets Each segment has unilateral genital pores For further details see Gradwohl and Kouri *(1948)*

The uterus quickly breaks up into parenchymatous egg capsules which completely fill the gravid proglottids and extend beyond the excretory vessels in a lateral field From 130 to 300 egg capsules may be counted in each gravid proglottid They are pressed so tightly against one another that they finally assume a polyhedral shape their diameter varies from 180 to 200 microns each capsule has 8 to 10 eggs The embryo measures 23 microns in diameter

Joyeux and Baer claim that *R (I) quitensis* León 1938 as well as all the new species described by Dollfus should be considered synonymous with *R (R) demerariensis* (Daniels 1895) The American species should thus be named

Raillietina (R) Demerariensis (Daniels 1895)

Synonyms —*R quitensis* León 1938 *R (I) luisaleoni* Dollfus 1939 *R (I) equatoriensis* Dollfus 1939 *R (I) leoni* Dollfus 1939 *R (R) le* Dollfus 1939

The life span is estimated at more than 10 and 15 years respectively in 2 cases reported by León These estimates were based on the length of time the patients had been expelling proglottids in their feces

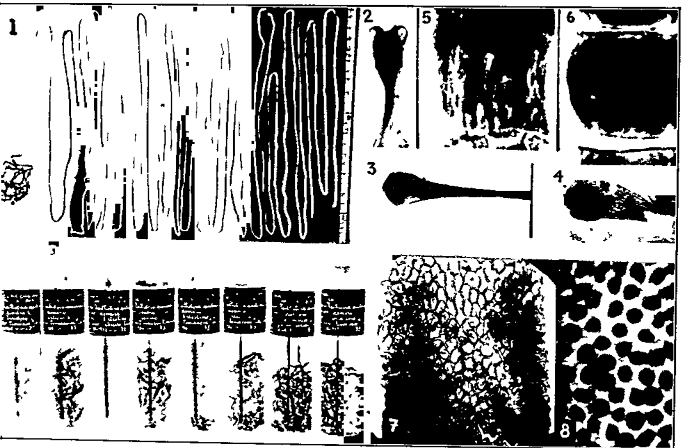


Fig 318 —*Raillietina quitensis* (L. A León 1938) *1* The parasite *2* *3* and *4* Scolices of the Ecuadorian species. *5* and *6* Proglottids from the anterior portion of the strobila. *7* Proglottid from the center portion of the strobila. *8* Proglottid from the caudal end *9* Eight specimens (Originals of León)

HOSTS AND GEOGRAPHIC DISTRIBUTION

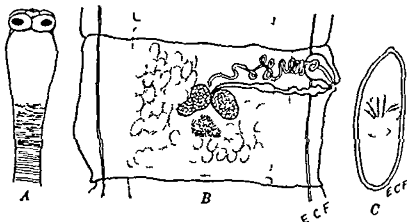
In 9 of 16 cases of nfestat on reported by León 5 pat ents ere women 3 ere ch dren and 1 was a man Later León descr bed 2 more ca es

The ntermed ate host and the b ology of t s spec es are not known Leon bel eves th the intermed ate host s to be found among the follo ng *Ped culus cap t s P vestimen Pulex irritans* and some small mollu ks Bul mus commonly calle l churros wh ch co st tute the favor te meal of the country people of the mounta nous reg on of the province P ch ncha and in Coleoptera *Leucop la a albescens* and *Heterogomphus bouc eri* common calle l catchos i Fuen lor The above ca es ere observe l n that reg on

Raillietina (R.) Madagascariensis (Davaine 1869) Joyeux and Baer 1929

Synonyms—*Taen a madagascar ens s* Dava ne 1869 *Da a nea madagascarien* (Dava ne 1869) Blanchard 1891

Th s paras te was l s overe l by Grenet n h ldren of the Con oro I lan l Several mo cas s were reporte l later As a Austral a and the Fa t In l es



F g 319—*I a et a R adagascar ens s* A Sco ex (after I ancha l in I ru pt I Matu e prog o t ×40) C matu e egg ×600 a a l f o a son y Faust Lece on s e Para olo la y Mel na Trop by I ou l an l Lasnu o court y of l tor I ron ax a S A Ha an a)

The adult paras te s 24 to 39 cm by 1 4 mm The s olex l as 4 large prox mal sucker v th very l ttle spa e for the rostellum l h is located among them an l wh l s p llo shape l The ro tellun s prov le l w th 90 to 110 hooklets n 2 ro s Al l ough the scol s well marked off from the bo l there s no v s ble neck the nonsegmented anter or port is sl ghtly ler than the s olex

The a lult paras te has 500 to 700 proglott ls The sexually mmature proglott ds a narro v the mature proglott ls are 1½ t mes w der than long The gravid proglott is a tw ce as long as w le

The *eggs* are fus form or ell pt cal about 5 l y 21 n crons The embryo or on l sphere is 8 to 15 n crons n d ameter and s prov ded w th 3 pa rs of lancet shaped hooklet

The life cycle of th s paras te is unknown but it s bel eved that cockroaches of th genus Per planeta ser e as ntermed ate hosts

Epidemi logy pathogenesis an l symptomatology of this parasitosis l av not as yet l een studie l

Diagnosis is made by obtaining the gravid proglottids of the parasite or by microscopic observation of the typical eggs

Ether extract of male fern has been used with good results in this parasitism

Proper **prophylactic methods** against this parasite have not as yet been studied

Raillietina (R.) Celebensis (Janicki 1902) Joyeux and Baer 1929

Synonyms.—*Davainea formosana* Akashi 1916, *Raillietina formosana* (Akashi 1916) Joyeux and Baer 1929

Only 2 human cases of parasitism by this cestode have been described, one in Japan, the other in Formosa. Rats serve as a reservoir for the parasite. This species is differentiated from *R. madagascariensis* in that it is larger, has more than 700 proglottids, the suckers lack hooklets, it has more oviferous capsules in each segment and there are more eggs per oviferous capsule. *The eggs are larger than those of R. madagascariensis measuring 99 by 46 microns*, while the hexacanth embryo is 12 to 14 microns in diameter. The life cycle is unknown. The epidemiology and symptomatology have not been studied as yet

Raillietina Asiatica (von Linstow 1901) Stiles and Hassall 1926

Synonyms.—*Taenia asiatica* von Linstow 1901, *Davainea asiatica* (von Linstow 1901) Braun 1903

This species was described from a study of a single specimen containing 750 proglottids but no scolex. It was expelled by a patient in Persia. The creation of a new species on the basis of only one incomplete specimen leaves much to be desired

SYMPTOMATOLOGY, DIAGNOSIS, AND TREATMENT

All species of Raillietinas found in human cases may be divided into 3 groups

1. African species, found in Madagascar and neighboring islands
2. Asiatic species, found in the Far East and the Netherlands and East Indies
3. American species, found in the Guianas and Ecuador

Joyeux and Baer claim that these 3 groups may be reduced to 2 distinct groups, differentiated as follows

1. African and Asiatic which would correspond to the species *Raillietina (R.) madagascariensis*
2. American corresponding to *R. (R.) demerariensis*

Symptomatology.—According to Leon the most marked symptoms are abdominal pain, nausea, intermittent diarrhea, dizziness, and mental sluggishness. There may be circulatory and nervous disturbances, anemia, and eosinophilia

Diagnosis.—Accurate diagnosis is easily made because the patients expel gravid proglottids in the feces

Treatment.—Leon has obtained good results with ethereal extract of *D. filix mas* along with calomel

Prophylaxis follows general measures

DIPHYLLOBOTHRIASIS (FISH TAPEWORM INFECTION)

(Parasitism Produced by the Adult Form of *Diphyllobothrium Latum*, Fish or Broad Tapeworm Infection)

Synonyms—Bothriocephaliasis dibothriocephalus anemia fish tapeworm infection, broad tapeworm infection

HISTORY

The Bothriocephalus was individualized as a distinct species by Plater de Basel (Switzerland) in 1602 Bonnet correctly described the scolex in 1777 differentiating it from *T solium*

It was observed in North America by Weinland in 1858 and by Leidy in 1879 in infected patients who had emigrated from Europe The first cases of American origin were reported by Ward in 1906 Nickerson 1906 1911 and Warthin in 1911 although several cases of doubtful origin had been found before this in 1895 in the states of the Great Lakes region

GEOGRAPHIC DISTRIBUTION

Since the intermediate hosts are dispersed throughout the world it is not strange that this parasite is also more generally encountered than formerly thought, although in fewer numbers in countries where fish is not eaten raw or partially cooked

This cestode is found in regions near the Great Lakes where the intermediate hosts are abundant, and where fish constitutes a major portion of the diet of the population It has been introduced into several foci in the lake regions of Minnesota southern Michigan and Manitoba and Nipigon Lake Ontario Canada No autochthonous human case of *Diphyllobothrium latum* infestation has been reported in Cuba although 2 cases have been reported One species found frequently in cats in rural districts another species in dogs are still to be classified

On 2 different occasions fragments of Diphyllobothrium expelled by children were sent to Kouri they were similar to those harbored by cats in Cuba

In Germany it has been seen in East Prussia it is also seen on the coast of Denmark and in Finland 30 per cent of the population in coastal regions are infected with 30 to 76 per cent infection in Karelia One hundred per cent of pikes and 51 to 82 per cent of perches in that country are infected (Petruschensky and Tarassow 1932) In Russia proper, Diphyllobothrium is frequent along the shores of the Baltic Sea in Leningrad and in Moscow In Archangel 74 per cent of the Russians and 95 per cent of the Samoyeds are infected In Sweden the parasite is found in the northern region of Argermann and Lapland In Holland it is less frequent In Italy it is found near Lakes Verese, de Monate, Ternate, and others, in Switzerland in Lake Geneva and Lake Neuchatel where 95 per cent of the burbots and 58 per cent of the perch as well as the pike are infected It is frequent in Romania where caviar from pike eggs is eaten raw in large quantities The parasite is rare in Belgium, France England and Spain In Asia *D latum* is found in Russian Turkestan, in Palestine, and in Japan In Africa the parasite is found in the lake N gami, in Ouganda and in the Belgian Congo It has also been reported in Madagascar

CAUSATIVE AGENT

Diphyllobothrium Latum (Linnaeus 1758) Luhe 1910

Synonyms—*Taenia lata* Linnaeus 1758 *T vulgaris* Linnaeus 1758 *T membranacea* Pallas 1781 *T tenella* Pallas 1781 *T dentata* Batsch 1786 *T grisea* Pallas 1796 *Bothriocephalus balticus* Kuchenmeister 1855 *B cristatus* Davaine 1874 *B latissimus* Bugnon 1886, *Dibothriocephalus latus* Luhe 1899 *Bothriocephalus taenioides* Leon 1916, *Dibothriocephalus minor* Cholodkowsky 1916

D latum is usually 3 to 10 meters long although it may be as long as 15 or 20 meters This species is very much smaller only 1 meter or less, in the intestines of dogs and cats which,

with man and other mammals, constitute the habitual or normal definitive hosts. The scolex is narrow, elongated, and flat, spatulate, or almond shaped. It is 2 to 5 mm. long and has 1 ventral and 1 dorsal long groove-shaped sucker or *bothrium*. The proglottids, small at first, increase progressively in size. They are usually much wider than long. The segments from the middle of the strobila to the caudal end are gravid. In the central part of each segment there is a dark lobulated mass which represents the uterus filled with eggs. The last 1/5 of the strobila is formed by mature and gravid proglottids. The genital pore is located in the center on the ventral surface. Beneath the genital pore there is a "laying orifice," or "tocostome," or uterine pore.

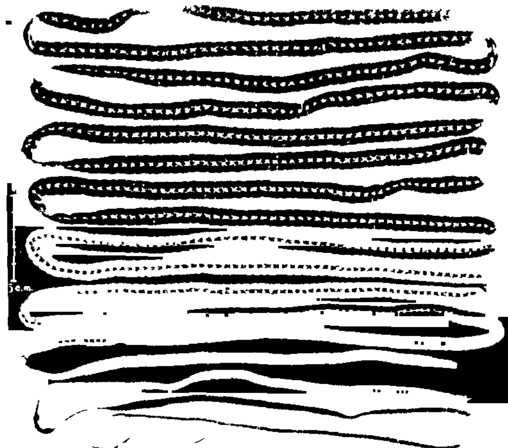


Fig. 320.—*Diphyllobothrium latum*. Complete adult specimen expelled during treatment. (Second case of Kourí, 1943, in Lecciones de Parasitología y Medicina Tropical by Kourí and Basnuevo, courtesy of Editorial Profilaxis S. A., Havana.)

The gravid proglottids of *D. latum*, by contrast with those of *T. saginata*, lay eggs until the uterus is empty. Then they contract and disintegrate, and the remnants are eliminated in the feces.

Eggs, 70 by 45 microns, may be found in great numbers in the feces. They are ellipsoid, have a brown-yellowish color, and are provided with operculated coverings. The operculum is relatively large and is found at the thicker pole of the egg.

Life Cycle

Diphyllobothrium inhabits the small intestine of man, dogs, cats, and other mammals. The eggs are passed in the feces and eventually enter water. Eleven to 15 days after reach

Fig 321 —*Diphyllobothrium latum* *Left* drawing of the adult parasite (after Leucka in Brumpt) *Right* Drawing of *1* scolex with *a,a* bothria *b* neck *2* cross section of th scolex *3* ventral surface of proglottids or segments showing the uterine rosettes with genital pore and *b* laying orifice (after Gulart)



Fig 322 —Egg of *Diphyllobothrium latum* (×400) (From the collection of R. B. H. Gradwohl

ing the water of proper temperature (15° to 25° C), ciliated hexacanth embryos, or coracidia develop. These force their way through the opercula and swim around in the water for 12 hours, then are ingested by certain small *crustaceans called Cyclops*. *In the Cyclops, the* embryos develop into primary larvae in 2 to 3 weeks and are known as procercoid larvae, which have a caudal sphere with 6 embryonal hooklets called cercomer. When these larvae are ingested by the secondary *intermediate hosts, fish, they bore through the intestinal* wall and become encysted in different organs. Here they develop into the secondary or pleocercoid larvae, or sparganum. Large fish are usually infected by eating small fish infected with these larvae. The secondary larvae pass into the intestines of the definitive host, man, dog, or cat, when the fish containing the parasites is eaten raw or poorly cooked. The scolex becomes attached to the wall of the intestine. Through proliferation of the scolex, the proglottids are formed, and finally the complete adult parasite, in 5 to 6 weeks, although after the second week eggs can already be found in the feces. The gravid proglottids deposit eggs which are eliminated in the feces to start a new cycle.

The *adult parasites* live in the small intestine of man, dogs, cats, seals, pigs, foxes, bears, and numerous carnivora, as well as in Pinnipedea and Cetaceae. According to Le Bas 40 to 95 per cent of certain fishes in Switzerland harbor the plerocercoid larvae in regions where the parasite is rare in man, which seems to indicate that in such regions man is not the principal definitive host of *D. latum*.

Number.—Usually the human host harbors only 1 or 2 specimens of the parasite, but 1 human case has been described in which 90 specimens were found, and 1 monkey was known to harbor 100 specimens of the parasite. According to Le Bas, 2 to 4 million eggs per gram of feces corresponds to one adult worm harbored in the intestines. Association of this parasite with *T. saginata*, *T. solium*, and *Diplogonoporus brauni* has been reported.

Life Span.—Riley described a case which harbored the parasite for at least 13 years.

PATHOGENICITY

The parasite is often well tolerated and causes only slight or no symptoms. Infestation with *D. latum* may produce the same disturbances as seen in taeniasis. In certain regions, especially along the coast of the Baltic Sea, this parasite frequently causes an acute anemia which resembles pernicious anemia.

Bothriocephalic Anemia

Patients show pallor and weakness, cardiovascular disturbances, such as edema, ocular hemorrhage, with marked pallor of the eyeground and of the optic nerve are also present.

There may be *gastrointestinal disorders such as vomiting and diarrhea*. The anemia is severe. See Chapter 68, Diphyllobothrium Anemia.

DIAGNOSIS

Diagnosis is established by direct microscopic examination of the feces where the eggs are found in great numbers. At times the patient expels long strobila.

PROGNOSIS

Diphyllobothriasis is usually benign and generally well tolerated. A small percentage of those who harbor the parasite develop an anemia similar to pernicious anemia, which usually disappears after expulsion of the parasite.

TREATMENT

Same as for taeniasis

PROPHYLAXIS

General Prophylaxis—Dissemination of the eggs of the parasite which are expelled by the millions with fecal material should be avoided Parasitized individuals should be found and cured as well as animals which harbor the parasite This is quite difficult to carry out because of the great numbers of animals which serve as definitive hosts

Drains and sewers should not open directly into rivers or lakes The waters from these sewers should be decanted and deposited in special depositories or filtered or disinfected with formalin or chlorine before the water reaches the rivers or lakes otherwise the first intermediate host (copepods) and the second intermediate hosts (fish) will be infested

The stools of parasitized individuals should be treated with sulfuric acid

Education of the public should be carried out

Individual Prophylaxis—Individual prophylaxis consists in avoiding eating fish which are poorly cooked It must be remembered that the larvae do not die unless they are boiled for 10 minutes They succumb in 48 hours if the viscera are placed in olive oil and lemon juice vinegar or covered with a saturated solution of salt

SPARGANIASIS

(Diseases Caused by Spargana or Larval Forms of Diphyllobothrium)

HISTORY

In 1882 Manson discovered the sparganum in the tissues of a patient autopsied in China Other similar larvae had been seen on numerous occasions in patients from China Japan Formosa French Indo China and less frequently in Africa (*S baxteri*) Java and Sumatra Holland British Guinea and Texas Larvae are morphologically not differentiable and are commonly found in the subcutaneous tissue between the muscles of frogs snakes birds and some mammals in foci of infection These spargana when extracted from the host and inoculated orally into dogs and cats developed different species but they were closely related to the Diphyllobothrium members of the subgenous Spirometra It is impossible to ascribe a name to species of Sparganum without experimental proof of its life cycle in a dog or cat and a study of the strobila of the adult which matures in the small intestines of these experimental hosts However *Sparganum mansoni* is usually the name which is given to the larval stage

In 193 1938 Mueller showed that *D mansonoides* which has its procercoid stage in *Cyclops leuckarti C viridis C bicuspidatus* and others a sparganum stage in the rat and in the Rhesus monkey and definitive stage in cats and dogs is the common species of the subgenus Spirometra in the United States

GEOGRAPHIC DISTRIBUTION

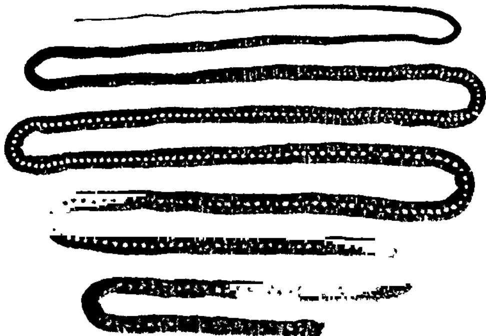
This cestode was first discovered in its larval form by Manson in 1882 at autopsy It is commonly known as Manson s cestode It is found quite frequently in China and Japan and has also been reported in Puerto Rico by Cram in 1926 and in New Orleans, La., by

Faust The adult parasite does not infect man (Faust, Campbell, and Kellog, 1929), but the larval forms, sparganum, of this and other similar species have been found in human parasitism in the Far East, most commonly in subcutaneous and ocular sparganiasis Several hundreds of human cases have been diagnosed to date in that region

CAUSATIVE AGENT

Diphyllobothrium (S) Mansoni (Cobbold 1882) Joyeux 1928

Synonyms —*Ligula mansoni* Cobbold 1882, *Bothriocephalus liguloides* Leuckart 1886, *Bothriocephalus mansoni* (Cobbold 1882) Blanchard 1888, *Dibothrium mansoni* (Cobbold 1882) Ariola 1900, *Sparganum mansoni* (Cobbold 1882) Guiart 1910, *Sparganum raillieti* von Ratz 1912, *Dibothriocephalus mansoni* (Cobbold 1882) Manson Bahr 1925, *Diphyllobothrium erinacei* (Rudolphi 1819) of Iwata 1933, *pro parte*



adult from cat experimentally infested with (tree toad) Note the central uterine rosette ottids and the almond shaped scolex (After Medicina Tropical by Kouri and Basnuevo

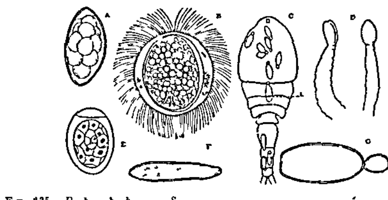
The *adult parasite* lives in the small intestines of dogs, woves, foxes cats, wild cats, leopards, and tigers When first seen, it resembles *D latum* It can be differentiated from the latter by its delicate structure, and lesser length, being only 60 cm to 1 meter long The scolex is 1 to 1 5 mm by 0 4 to 0 8 mm The free borders of the bothria are well developed The proglottids are wider than long, except for the gravid proglottids which are almost square The eggs vary in size, 52 to 68 5 by 32 to 43 5 microns

The sparganum of *D mansoni* is much larger than that of *D latum* A great number of animals serve as secondary intermediate hosts for the parasite frogs, snakes, birds, and mammals, including man


0
50μ

Life Cycle

The life cycle is quite similar to that of *D latum* The first intermediate host is a eucopepodan crustacean, the second is a vertebrate, and the definitive host is also a vertebrate The *eggs* are passed in the stools of the definitive host The embryo completes its development in 5 weeks in water, then forces its way through the operculum and swims freely When ingested by its first intermediate host, *Cyclops leuckarti* the embryo gains access to the cavity of the Cyclops and is transformed into a procercoid larva If the Cyclops is ingested by the second intermediate hosts, frogs, snakes, birds, or mammals, it is partially digested in the stomach and liberates the procercoid larva The larva bores through the gastric wall and migrates toward the deep muscles although at times it remains in the iliac fossa, pleural cavity, lumbar region, urethra, etc In these regions, the larva becomes a sparganum It can be differentiated from the sparganum of *D latum* only by its larger size The multiplication of the larvae by gemmation now takes place The number of larvae that are produced at this time depends entirely upon the amount of available space and the nutrition which the primitive larvae command When the definitive host, dogs, cats, and wild animals ingest the second intermediate host, the sparganum is transformed into an adult parasite of the intestinal tract



A Egg ... *Cyclops* ... oid larva. ...) (After ... courtesy of Editorial Profilaxis S A Havana)

To date it is considered that man may become infected exclusively by the larval form of sparganum of this parasite Although it has not been proved, it is quite probable that man acquires somatic or visceral sparganiasis as a result of drinking water containing Cyclops contaminated with the procercoid larvae of the parasite Most of the human case histories reported in the Far East mention the use of flesh of the second intermediate host generally frogs, as poultices over some inflamed or suppurated area of the body (Joyeux and Houdemer, 1928, Faust, Campbell, and Kellog, 1929)

SYMPTOMATOLOGY

A number of cases of human sparganiasis have been reported in which nonramified larvae have been obtained generally in the muscles, connective tissue or in the orbital region If the infection is caused by ingestion of infected Cyclops it will, of course, be mild and consequently asymptomatic from the time the larvae enter the stomach wall and begin their migration until they localize As the larvae develop the area becomes edematous and very sensitive to touch When the lesion is incised, a purulent or chylous exudate

is liberated in which at times the spargana may be found. They are recognized by their active movements consisting of contractions and elongations. At times the spargana undergo caseous degeneration. The death of the larvae causes a severe inflammatory reaction.

The most frequent mode of human infection and the only one that has been proved is by the application of packs of the flesh of the second intermediate host of the parasite contaminated with sparganum to some region of the body. Upon contact with the warm human body the larvae leave the pack and bore into the tissues at that site.

The presence of the larvae in or around the eye, ocular sparganosis, is characterized by severe pain with irritation and edema of the eyelids and much lacrimation. In the case of subconjunctival infections toxemia of the region is produced and gives rise on some occasions to the formation of nodules around the worm. Lagophthalmus and ulceration of the cornea are the results of retrobulbar invasion by the larvae.

DIAGNOSIS

Diagnosis can be made only by incising the lesion and obtaining the nonramified sparganum which frequently adheres to the tissues by its scolex. It should be differentiated from *S. proliferum* which is irregular in shape and ramified. Nevertheless there are other species of sparganum similar to *D. mansoni* which are also unramified and which are differentiated only when the adult parasite can be obtained from dogs, cats and other definitive hosts by *experimental feeding*.

TREATMENT

Treatment consists, when possible, of extirpation of the larvae and drainage of the region.

Cornet in 1933 recommended injecting 2 to 4 c.c. of ethyl alcohol with novocain to kill the larvae *in situ*. They are later extirpated or are left to be absorbed.

Keller in 1937 reported excellent results with intravenous injections of Novarsenobenzol 0.[illegible]0 to 0.45 Gm. per dose for adults, 0.07 to 0.15 Gm. for children, every 4 or 5 days in 2 to 6 doses. Tarsorrhaphy has been used to preserve the cornea until the worm is absorbed or eliminated.

PROGNOSIS

Prognosis depends upon the localization of the larvae in the human host as well as the facility with which they can be extirpated without injuring vital organs.

PROPHYLAXIS

Prophylactic measures consist in boiling or filtering drinking water in regions in which the parasite is endemic and in avoiding the local application of frog flesh or flesh of other vertebrates infected with sparganum to ulcers or inflamed regions.

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CHAPTER 43

TREMATODIASIS OR DISEASES CAUSED BY FLUKES (PARAGONIMIASIS FASCIOLOPSIASIS HETEROPHYIASIS METAGONIMIASIS ECHINOSTOMIASIS CLONORCHIASIS OPISTHORCHIASIS HUMAN FASCIOLIASIS HEPATICA)

Pedro Kouri

Trematodes are flatworms with smooth integument unsegmented body incomplete digestive tract and no anus The shapes vary but they are usually leaf like All the Distomata except Schistosoma are hermaphroditic

DISEASES CAUSED BY LUNG FLUKES

Paragonimiasis

(Diseases Caused by *Paragonimus Westermani* Pulmonary Distomiasis Endemic Hemoptysis Oriental Lung Fluke Infection)

HISTORY

Paragonimus westermani was found in 187? by Westerman in the lungs of a dead tiger in the Zoological Garden of Amsterdam In 18?8 Kerbert made a study of the parasite to which he ascribed the name *Distoma westermani* In 18?9 Ringer found it in lungs removed at autopsy from a Portuguese who had died in Formosa Cobbold in 1880 named it *Distoma ringeri* In 1880 Manson discovered the eggs in the sputum of a Chinese resident of Formosa Other investigators noted the parasite and its eggs in Chinese Japanese and Filipinos (Baelz (1880 1883) Yamagiwa (189? Musgrave 190? and others

Nakagawa was the first to study the life cycle (1915) Later Nakagawa Yokogawa Kobayashi and others Japan (1915 19?1 and more recently Vogel Wu Watt and Chen (1935 193? in China and Ameel in 1934 in North America studied the life cycle

The American form *Paragonimus kellicotti* was described by Ward in 1894 in a cat in Michigan

GEOGRAPHIC DISTRIBUTION

This parasitic disease originates in the Far East where it is widely distributed especially in China Korea the Philippine Islands Japan Indo China and Formosa It is endemic in Japan the mortality rate being very high Africa India Brazil (Mato Grosso) Peru Yucatan Venezuela Ecuador and the United States of America have also been reported as foci of infestation

CAUSATIVE AGENT

Paragonimus Westermani (Kerbert 1878) Braun 1899

Synonyms—*Distoma westermani* Kerbert 18?8 *Distoma ringeri* Cobbold 1880 *Distoma pulmonum* Baelz 1880 *Distoma pulmonis* Kiyoma 1881 *Distoma fusca* Baelz 1881 *Distoma pulmonale* Baelz 1883 *Distoma ba?* Cobbold 1884 *Distoma westermani* Leuckart 1889 *Distoma cerebrale* Yamagiwa 1890 *Mesogonimus westermani* Railliet 1890 *Polysarcus westermani* Looss 18?9 *Paragonimus kellicotti* Ward 1908

Common Names Lung distome causative factor in pulmonary distomiasis parasitic hemoptysis endemic hemoptysis or paragonimiasis

P westermani is the causative agent of pulmonary distomiasis (distomatosis) or parasitic hemoptysis in man

The *worm* is 8 to 16 by 4 to 8 by 3 to 4 mm It is reddish brown and when kept in alcohol is the shape and size of a coffee bean The oral sucker is subterminal, the ventral sucker *is a short distance in front of the center of the parasite* The suckers are large and almost the same size (1 to 1 4 mm)

The body of the parasite is covered with broad spines which vary in shape The spines between the two suckers resemble a cluster of scales

The eggs are operculated, ovoid reddish brown *85 to 100 by 50 to 60* microns They are abundant in the sputum and less frequently found in the feces

Life Cycle

The egg is coughed up in the sputum and eventually deposited in water, where it gives rise to a miracidium which escapes through the operculum This phase of the development requires 2 weeks in summer and 8 weeks in winter

If the miracidium finds the primary intermediate host (species of snails of the genera Melanida, Hua, Semisulcospira (Brotia), Tarebia, Assiminea, Pomatiopsis, and Pomacea) it penetrates into the body and forms a sporocyst beneath the epidermis This sporocyst produces rediae which in turn give rise to daughter rediae These daughter rediae become localized in the hepatopancreas, where they produce cercariae, provided with a tiny stylet They leave the body of the snail then penetrate into the body of several species of crayfish and crabs They encyst in the muscles of these crustaceans rarely in the liver and in the legs, but never in the gills as formerly believed The metacercariae are able to infest their definitive hosts from 42 to 45 days after they have become encysted When these infesting cysts are ingested by cats or dogs the immature parasites leave the cysts enter the small intestine, perforate its wall and gain access to the abdominal cavity They migrate to the thoracic cavity where after 30 days they bore through the pleura and the lung tissue and finally settle in the bronchioles where they are found in pairs They develop into adult forms which encyst between the hypertrophied walls of these ducts

Man is infested by eating raw or half cooked crustaceans containing the parasitic cysts

About 9 species of snails are commonly primary intermediate hosts in the Far East In Venezuela, the most commonly infested species is *Pomacea luteostoma* according to Iturbe and Gonzalez although this has not been confirmed, in North America *Pomatiopsis lapidaria* is the most common host for *P kellicotti*

Crayfish and crabs which act as secondary intermediate hosts are members of the following genera *Parathelphusa Potamon, Eriocheir, Cambarus and Sesarma in the Orient Pseudothelphusa iturbei* in Venezuela and various species of the genus Cambarus in North America The definitive hosts in addition to man, are cats, dogs hogs, and mongooses

SYMPTOMATOLOGY

The first stages of the disease are characterized by the presence of blood stained sputum and even hemoptysis Later chronic cough develops especially in the morning The sputum resembles that in lobar pneumonia Hemoptysis of variable intensity may recur, often lasting for several days Some cases show symptoms similar to those of tuberculosis Erratic localization of the parasite in the brain is very rare When infestation of the brain occurs, the patient suffers epileptiform spells At autopsy the lung surfaces may show a variable number of hard cysts which may reach the size of a pea These cysts contain parasites usually in pairs and a variable quantity of a reddish purulent liquid with numerous eggs One may find at times large numbers of eggs in cysts if the parasite dies and has disintegrated Micro

scopic investigation shows that the cysts are formed in the small bronchioles which become hypertrophied and obliterated their walls becoming sclerotic and infiltrated with cells of inflammation The epithelium becomes stratified (metaplasia)

In intestinal paragonimiasis the cysts localize in the intestinal wall causing diarrhea Eggs of the parasite are found in the stools The cysts can develop in the abdominal glands producing clinically febrile pictures or in the skin and subcutaneous cellular tissue with abscess formation

In endemic zones in Japan cerebral symptoms in children less than 15 years of age have been mistaken for infantile paralysis cerebral hemorrhage encephalitis and meningitis

The parasites also localize at times in the liver muscles testes peritoneum and pleura where they can be recognized by their characteristic dark blue color

DIAGNOSIS

Diagnosis is made by examination of the sputum using direct slide cover slip preparations The sputa are frequently stained with blood and show rust brown flakes composed of clusters of eggs of the parasite Differential diagnosis should be made from bronchopneumonia tuberculosis bronchial spirochetosis and pleural effusion Cysts in the lungs can be seen on x ray examination

The eggs can be found in small numbers in the feces if the sputum is swallowed or in diarrheal stools if the parasite localizes in the intestines They are seen at times in pus from subcutaneous abscesses caused by the parasite

TREATMENT

There is no known specific treatment Tartar emetic should be used since it has proved efficacious in some cases by improving the clinical picture Emetine also has been used Surgery of the lung has been recommended in cases of superficial cysts which are easily accessible Tonic medication should be used in all cases to help restore defenses of the patient The patient should be removed from the endemic zone to prevent reinfestation Some years after leaving the endemic zone the patient may regain his health due to spontaneous death of the parasites which slowly disintegrate and at times are expelled in coughing

PROPHYLAXIS

General prophylaxis consists in preventing dissemination of the eggs in sputum and feces by instructing patients to collect all their specimens (sputum feces) in special containers so that the eggs may be properly destroyed with sulfuric acid All parasitized animals (dogs cats hogs rats) should be destroyed thereby preventing dissemination of the eggs by these animals The contaminated viscera of pigs should be destroyed by sulfuric acid Mollusks should be destroyed or controlled through proper measures

The individual should avoid eating raw or imperfectly cooked crayfish and crabs

DISEASES CAUSED BY INTESTINAL FLUKES

1 Fasciolopsiasis

(Disease Caused by *Fasciolopsis Buski*, the Giant Intestinal Fluke)

HISTORY

Fasciolopsis buski was discovered by Busk in 1843 in the duodenum of a sailor autopsied in London It has been described since then under several different names, due to the variety of forms and sizes which it usually presents

GEOGRAPHIC DISTRIBUTION

In certain foci of Central and Southern China, Formosa, Indo China, Siam, Borneo, Sumatra, Assam, and Bengal, this is a common parasite of man and pigs It is also found in other regions of the Far East In Canton, only a small percentage of dogs is infected, since dogs seem to be partially resistant to this infection

CAUSATIVE AGENT

Fasciolopsis Buski (Lankester 1857) Odhner 1902

Synonyms—*Distomum crassum* Busk 1859, *Distomum rathousi* Poirier 1887; *Opisthorchis buski* R Blanchard 1895, *Fasciolopsis rathousi* (Poirier 1887) Ward 1903, *Fasciolopsis fulleborni* Rodenwaldt 1909, *Fasciolopsis goddardi* Ward 1910, *Fasciolopsis spinifera* Brown 1917

The *adult worm*, which attaches itself to the walls of the duodenum and jejunum, is a large fleshy parasite, oval but usually elongated and ovoid Its size is variable 20 to 75 by 8 to 20 by 0 5 to 3 mm The surface of the parasite is covered with spines The cephalic cone is absent The oral sucker is about 0 5 mm, while the ventral sucker is approximately 3 mm in diameter For further details, see Gradwohl and Kouri (1948)

The *eggs* are quite similar to those of *Fasciola hepatica*, 130 to 140 by 80 to 85 microns, *and are operculated They do not contain a developed miracidium when laid The life cycle of* the parasite was described by Nakagawa (1921) in the pig and by Barlow (1925) in man It is similar to that of *F hepatica*

Life Cycle

The eggs are passed in the feces of the definitive host It requires 3 to 7 weeks at 26° to 32° C for the miracidium to develop When it reaches maturity, it forces the operculum open and swims freely until it finds an appropriate host, a snail It penetrates the soft tissues of the snail and in a few weeks gives rise to sporocysts, rediae, and cercariae The molluscan hosts in China and Formosa are *Planorbis caenosus, Segmentina nitidella, S calathus, S hemisphaerula Hippeutis schmackeri, H cantori*, and *Gyraulus saigonensis* The cercariae are similar to those of *F hepatica* In endemic regions the cercariae encyst in the roots and bulbs of certain aquatic plants Man is infected by husking the infected plants between the teeth and lips, before eating the contents The metacercariae leave the cyst in the duodenum and cling to the walls of the intestine, where they grow to the adult stage in about 3 months Human infection is associated with eating certain uncooked aquatic plants cultivated in endemic areas where the appropriate host is abundant

SYMPTOMS

Although the parasites usually localize in the duodenal mucosa it is not uncommon to find them attached to the mucosa of the pylorus or even to the mucosa of the large intestine When the parasites adhere to the intes

tinal wall, they first cause an inflammatory reaction and later ulceration The capillaries of the wall may be eroded, resulting in hemorrhage Abscesses of the wall may also be produced In massive infections, an acute abdominal picture may result

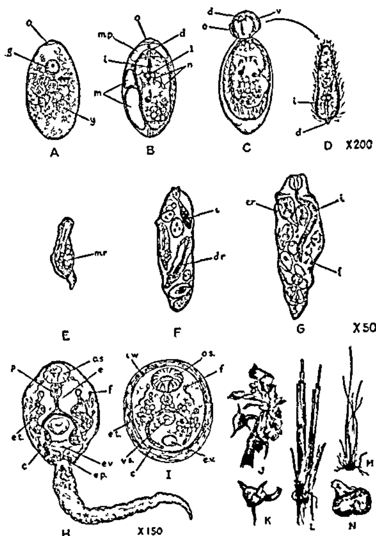


Fig 326—*Fasciolopsis buski* larval forms *A* Undeveloped *B* miracidium within the egg *C* miracidium leaving the egg *D* miracidium (*A*, *B*, *C*, *D* in the water) *E*, sporocyst *F*, mother redia *G* daughter redia (*E* *F*, *G* within the mollusk) *H*, cercaria *I*, metacercaria *J* *Trapa natans* water caltrop *K* fruit of *Trapa natans* *L* water bamboo (*Zizania aquatica*) *M*, water chest[illegible] (*H* to *N* in the water) *c* ceca [illegible] the miracidium *d r* daughter re[illegible] cretions *e t* excretory vesicle [illegible] *i w* inner cyst wall *l* optic lens [illegible] which mother redia develops *n* [illegible] vitelline membrane *v s* ventral s[illegible] redrawn from Wu 1937 by Hell[illegible] Parasitologia y Medicina Tropical (5) Kouri and Basnuevo.)

The first symptoms appear near the end of the incubation period They are diarrhea and painful hunger In mild infections these may be the only symptoms When the number of parasites is large the case may simulate gastric ulcer with an asthenic state Symptoms of general intoxication may appear such as edema of the face abdominal wall and lower extremities At times there is ascites with diffuse abdominal pain The diarrhea which at first alternates with periods of constipation becomes persistent and the stools are a yellow green mass with a pungent odor containing large amounts of undigested food Although at times the appetite remains unchanged anorexia nausea and vomiting are frequent In advanced stages the skin is dry and rough a state of extreme prostration develops Death is due to toxemia followed by anasarca

Young in 1934 found that 42 5 per cent of the cases showed leucocytosis with eosinophilia and neutropenia At times there is lymphocytosis The erythrocytes do not seem to be altered

DIAGNOSIS, PROGNOSIS, AND TREATMENT

Diagnosis is based on finding the eggs in the stools In endemic regions the history of the disease may be important, however one should exclude fasciolíasis and echinostomiasis

Prognosis is good in early cases if the patients are treated in time but it is serious in the final stages of the disease

Drugs used are beta naphthol carbon tetrachloride and hexylresorcinol the latter being the drug of choice

PROPHYLAXIS

Prophylactic measures consist in dipping raw vegetables in boiling water for several seconds or peeling and washing them in clean water Snails can be killed by using a 1 50 000 solution of copper sulfate in fields covered with water Since most of the endemic foci are maintained by using human feces as fertilizer sterilization of the feces should constitute the fundamental prophylactic measure

2 Heterophyiasis

(Disease Caused by *Heterophyes Heterophyes* and Other Species of the Genus)

HISTORY

Heterophyes heterophyes was discovered by Bilharz in Cairo in 1851 in the intestine of an Egyptian child von Siebold called it *Distoma heterophyes* Cobbold in 1866 established the genus Heterophyes Looss in 1894 gave the first description of the type species he also found that the disease was frequent in Egypt the eggs passing undetected because of their small size Leiper found it in two sailors one Chinese the other Japanese in a London hospital and established its existence in the Orient Onji and Nishio in 1915 described an almost identical parasite in Japan and called it *Heterophyes nocens*

GEOGRAPHIC DISTRIBUTION

The parasite is found in Egypt Palestine in central and southern China Japan Korea Formosa and the Philippines

CAUSATIVE AGENT

Heterophyes Heterophyes (von Siebold 1852) Stiles and Hassall 1900

Synonyms —*Distoma heterophyes* von Siebold 1852, *Distoma heterophyes hominis* Diesing 1855, *Dicrocoelium heterophyes* Weinland 1858, *Fasciola heterophyes* Moquin Tandon 1860, *Heterophyes aegyptiaca* Cobbold 1866, *Mesogonimus heterophyes* Railliet 1890, *Coenogonimus heterophyes* Looss 1899 *Cotylogonimus heterophyes* Luhe 1899 *Heterophyes nocens* Onji and Nishio 1915

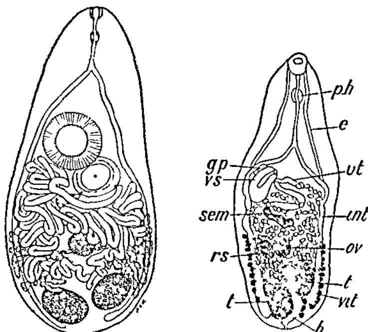


Fig 37 —1, *Heterophyes heterophyes* (after Mönnig) 2 *Metagonimus yokogawai* (after Ciurea) Adult of each species ventral face In *H heterophyes* 1 the posterior extremity is thicker than the anterior Note the larger ventral sucker (acetabulum) and ... ital sucker The ... testes are oval posterior and ... n te *b* excretory vesicle *e* excretory canal *gp* ... ary *ph* pharynx *rs* seminal receptacle *sem* ... it vitelline *vs* ventral sucker or acetabulum ... le Parasitologia y Medicina Tropical courtesy of



Fig 38 Egg of *Heterophyes heterophyes* Camera lucida drawing (Original figure in Faust Human Helminthology 1939 courtesy of Lea & Febiger)

The parasite is very small approximately 1 5 by 0 5 mm The oral sucker is small and subterminal the ventral sucker is almost 3 times larger and slightly excentric

The *eggs* are small brownish, and have a thick shell They measure 26 to 30 by 15 to 17 microns This worm is a habitual parasite of dogs cats rabbits, man, and other animals.

It completes its cycle in 2 intermediate hosts, the first a salt water mollusk, *Pirenella conica* (Khalil, 1933), which can also be found in brackish water The second intermediate hosts are fish of the family Mugilidae, especially mullets, in the muscles of which the infective metacercaria for man and other definitive hosts becomes encysted Man and other carnivora acquire the parasite by eating contaminated fish The adult parasite lives in the small intestine and cecum of its definitive hosts, generally in great numbers

SYMPTOMS

Its pathogenic role is insignificant in animals and seems to be of little importance in man

TREATMENT

The usual anthelminthics may be used Care should be taken to administer the anthelminthic after complete evacuation of the bowels If this is not done, it cannot act on those trematodes which, because of their extremely small size, can protect themselves against the treatment by lodging in the intestinal villi

PROPHYLAXIS

Prophylactic measures consist in cooking fish well in countries where the parasite abounds

3 Metagonimiasis

(Disease Caused by *Metagonimus Yokogawai*, Yokogawa's Fluke)

HISTORY

In 1911 Yokogawa found a larva of the trematode encysted in the tonsils, scales, and muscles of certain fresh water salmon in Formosa This parasite, *Metagonimus yokogawai* was described for the first time by Katsurada in 1912, who succeeded in experimentally producing the adult trematode, noting that the eggs are similar to those found in human feces He called attention to its wide distribution in Japan It was reported by Kobayashi in 1912 in Korea, by Yokogawa in 1913 in Formosa, and in 1915 by Ciurea in Romania

GEOGRAPHIC DISTRIBUTION

This is a common parasite of man in Egypt and the Orient (Japan, China, Korea, and Formosa) It is found in Siberia, Palestine, Russia, and the Balkans It has been reported in Spain by López Neyra and Pozo (1932), and in Romania by Ciurea

CAUSATIVE AGENT

Metagonimus Yokogawai Katsurada 1912

Synonyms —*Heterophyes yokogawa* Katsurada 1912, *Loxotrema ovatum* Kobayashi 1912 *Tocotrema yokogawai* Katsurada 1912, *Metagonimus ovatus* Yokogawa 1913, *Yokogawa yokogawai* Leiper 1913, *Loosia romanica* Ciurea 1915, *Loxotrema ovatum* Kobayashi 1908 (erratum) of Leiper 1922

The adult parasite is very small, 1 to 2 5 by 0 4 to 0 75 mm The body is pyriform The posterior extremity is rounded, the anterior narrowed and covered with scales The ventral sucker is larger than the oral and is to one side of the median line

For further details, see Gradwohl and Kouri (1948)

Eggs are brownish yellow, operculated, ovoid, 28 by 17 microns They are differentiated with difficulty from those of Heterophyes When laid, they contain a completely developed miracidium

Life Cycle

The first intermediate hosts of *M. yokogawai* are *Melania libertina* and *M. ebenina* within which the sporocysts, rediae and cercariae are formed. These leave the snail and swim freely in the water until they reach an appropriate host. They bore under the scales and into the muscles of fish, the second intermediate hosts. The most common intermediate hosts in Japan are the fresh water fish *Plecoglossus altivelis* and *Leuciscus hakuensis*. When they enter the fish the cercariae lose their tails and in the muscles or under the scales they secrete a cystogenic substance which forms a membrane around them. The encysted larvae grow according to the quantity of nutritive material available and the length of time they have been within the fish.

Man is infected by eating raw contaminated fish. In the duodenum the young distome breaks through the cystogenic membrane which protects it as it passes through the stomach and adheres to the intestinal mucosa where it grows into an adult parasite.

SYMPTOMS

The pathogenic role of this parasite is very mild and the symptoms to which it gives rise are insignificant. Nevertheless in massive infestations mild intestinal disturbances and even persistent diarrhea may appear.

Africa and his co-workers considered this parasite capable of producing more marked symptomatology. At times the eggs of the parasite filter through the intestinal wall and enter the lymphatics where they pass into the general circulation in large numbers. They may stop in the blood vessels of the myocardium or in the valves of the heart and give rise to a cellular reaction which initiates cardiac disturbances with syndromes easily mistaken for beriberi. The eggs are sometimes carried to the spinal cord or to the brain where they cause severe motor and sensory disturbances.

DIAGNOSIS

Diagnosis is based on finding the eggs of the parasite in the stools where they must be differentiated from those of *Clonorchis sinensis* and *Opisthorchis felineus*.

TREATMENT

The parasite usually leaves the definitive host spontaneously. The following drugs have been used with favorable results: carbon tetrachloride, *tetrachloroethylene* and *ether extract of male fern*.

PROGNOSIS

Prognosis is favorable unless the eggs pass into the general circulation and come to rest in the heart or in the nervous system of the definitive host.

PROPHYLAXIS

Human infection can be avoided if fish are thoroughly cooked before eating.

4. Echinostomiasis

(Disease Caused by *Echinostoma ilocanum*, Garrison's Fluke)

HISTORY

This parasite was discovered in the Philippine Islands by Garrison in 1908, in a native of Luzon. This author first found the eggs in human stools, and later obtained, during treatment, specimens of the adult parasite, expelled by a native prisoner. Odhner, after detailed study, placed it in the genus Echinostoma in 1911. Tubangui and Pasco in 1933 clarified the complete life cycle of *the parasite, Tubangui (1931) demonstrating that the gray rat, Mus norvegicus,* is the natural reservoir of the parasite in the Philippines. It has also been experimentally demonstrated that white rats, cats, and monkeys are also appropriate definitive hosts. Chen in 1934 showed that in Canton 13.5 per cent of the dogs harbored the parasite. Brug and Tesch (1937) believed that they had found the Echinostoma in the natives of Dutch East Indies.

GEOGRAPHIC DISTRIBUTION

Echinostoma is found in mammals in the Philippines and China. The area of human infection is limited to the Ilocanan population of the Province of Luzon, the Philippines, the Celebes, Java, Assam, and Japan.

CAUSATIVE AGENT

Echinostoma Ilocanum (Garrison 1908) Odhner 1911

Synonyms.—*Fasciolctta ilocanum* Garrison 1908, *Euparyphium ilocanum* (Garrison 1908) Tubangui and Pasco 1933.

This is a small trematode, reddish gray, oval, and elongated. It is 2.5 to 6.5 by 1 to 1.35 by 0.5 to 0.6 mm. On the anterior extremity, the parasite shows a circumoral disc, separated from the body proper by a slight constriction. The adoral disc is 0.22 to 0.34 mm wide and bears a crown of 49 to 51 spines. The integument is covered with scales which extend to the level of the posterior ovary. The oral sucker is small, 0.10 to 0.16 mm in diameter, and lies in the center of the adoral disc. The ventral sucker or acetabulum is larger, 0.40 to 0.46 mm in diameter, and lies at the beginning of the widened portion of the body.

For further details, see Gradwohl and Kouri (1948).

The *eggs* are ovoid and operculated, 83 to 116 by 58 to 69 microns. When they are passed in the feces they do not harbor a miracidium; this develops in the water within 6 to 15 days after the eggs have left the body.

The adult parasite inhabits the anterior part of the small intestine of its definitive host, usually attached to the mucosa by means of its crown of spines.

Life Cycle

The larval cycle takes place in 2 intermediate molluscan hosts. The first host is the snail, *Gyraulus prashadi*, which is penetrated actively by the miracidium. On reaching the *digestive gland the miracidium develops into a sporocyst; within the sporocyst the mother* rediae, and within these the daughter rediae, develop; these produce cercariae within 42 to 50 days after invasion of the snail. The cercariae leave the snail and may become encysted on any fresh-water snail, but the second habitual or natural intermediate host is *Pila luzonica, frequently eaten raw by natives.* Some become infected when they inadvertently ingest metacercariae along with the snails.

SYMPTOMS

The parasite causes no symptoms in the digestive system.

TREATMENT

Male fern is a specific in the treatment of this parasitosis.

PROPHYLAXIS

Prophylaxis is the same as for other trematode diseases.

DISEASES CAUSED BY LIVER FLUKES

1 CLONORCHIASIS (CHINESE LIVER FLUKE INFECTION)

(Disease Caused by *Clonorchis Sinensis* the Chinese Liver Fluke)

HISTORY

The *Clonorchis sinensis* was discovered by McConnell in 187_ in the biliary passages a Chinese pat nt in Calcutta C lbold named it *Dist ma s nense* in 18 _ Var ous ca were reported among the Chinese in Maur t us Ba lz in 1883 des ribed tw o species in Jap one small the other large but cons dered only the small spec es pathogenic Lat r he ec cluded that they were different f rms of the sa e spec es Ch en Pang in 19_3 prov definitely that the difference in s ze was s mply a var at on within the species Blan ha 189 created th genus Op i th r h n l el genus th parasite was clas fied unt l 19 Looss in 1 0 establ sh d the genus Clon r h s Saito n 18 8 was the first to observe t m r c d u Kobayash 1911 191 experimentally recovered the adult worms from mamm which had been fed fresh water fi h conta n ng the encysted cercariae Muto in 1918 iden fied the first intermediate h st when he foun l the cercar e in fresh water mollusks Faust a Khaw in 192 made a study of the b ology of the para te and of the ep d m ology of t infect on in China

GEOGRAPHIC DISTRIBUTION

This trematode is a parasite of mammals h ch feed on fi h n Japan Ch na Formo Kor a and French Indo Ch na The pr c p l fo us of human infect on is found in Okayar (Japan) southern K rea Kwangtung Ch na and the R d River delta n French In Ch na It is practically n nex stent in northern Ch na Em gration has not resulted establ shment of new foc f fection sin no adequate nterme iat hosts have been fo to ex st in oth r ountries Many cases have been reported among the Cantone e in Cub Ph l a d Hawa The presence of the dis ase among Hawa ans has be n expla n by th f t that th y at r f t f h imp rt d from Ch na r Japan

CAUSATIVE AGENT

Clonorchis Sinensis (Cobbold 1875) Looss 1907

(The Chinese Liver Fluke)

Synonyms—*Distoma sinense* Cobbold 18 *D toma spathul tum* Leu kart 18 *D st ma hep ti a nn cuum* Baelz 1883 *D st a hepat s en lem um* B elz 1883 *D stoi hep t c p rn ciosum* Baelz 1883 *D st ma end m cum* Ijima 1886 *Dist ma japonicum* Blanchard 1886 *Op sth rchis s nens s* Bl nchard 18 _ *Cl nor his end m cus* Looss 190 *pro parte* *Cl n rch s sinens s* var *maj r* Verdun and Bruyant 1908 *Cl norchis s nens s* va *minor* Verdun and Bruyant 1 8

In Cuba there is a larg Ch ese l v c n entrated princ pally in the city of Havan The majority f these Ch nese are Cantonese om ng from one of the m t ant nse endem f c of clon r h as s According to Kour Bas nue a d Sotolongo (1940) 93 per cent the Ch ese wh have l ed in Havana sho ed paras tes in the b le ducts the hab tual locali ti n According to stat stics by Kouri Bel r Am l and Basnuevo (1936) 5 per ce of th Ch nese res d nts of C ba Havana with ut apparent sympton s r w th only m sympt ms sh wed eggs f C sinens s n the stools According to Kouri and Kra le 4 p ent f Ch n se in Cuba with d gest ve and hepatol lary d sturbances with a general nervo state are paras t zed by the Ch nese l ver fluke wh ch has been proved by ser al coprol g exam at If xa at ns had been made of concentrated stools and b le obta ned l duod nal ntubat n meth d of Kouri the percentage of paras tism w uld probably ha been eve greater

Th l st e s tra sparent and elongated with a th nner anter or than poster r e trem ty Wh n exami n f esh n s me spec ens are wh t h h l others are brown l mo



Fig 379.—*Clonorchis sinensis* *1* and *2* Photographs of the parasite *1* natural size and, *2* slightly enlarged *3* Photomicrograph of a specimen stained with Meyer's hemalum (×12) *4* and *5* Eggs in bile obtained by duodenal intubation (Originals of Kouri)

or less dark Both forms may be present in the same liver The parasite is 2 cm by 4 mm For further details see Craig and Faust (1948)

The *eggs* are small 25 to 30 by 15 to 17 microns characteristically pyriform the *posterior extremity being broader than the anterior In the center of the posterior end there* is a small bud A prominent operculum is seen at the narrower anterior end It has a single yellowish colored covering It contains a completely developed miracidium when laid

Life Cycle

The adult parasite lives in the bile ducts of man dogs cats swine rats and certain wild carnivorous animals of the Far East which are the definitive hosts

The egg containing a miracidium is passed with the feces of the definitive hosts While some claim that the miracidium hatches in the water and then penetrates into the mollusks (first intermediate hosts) others notably Faust believe that hatching actually

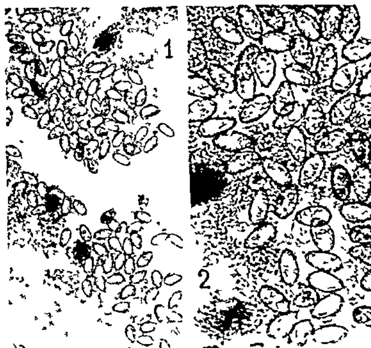


Fig 330—*Clonorchis sinensis* eggs in human bile obtained by duodenal intubation 1 ×160 2 ×320 (Original photomicrographs of Kouri)

occurs in the esophagus of the mollusk when it swallows the egg later sporocyst rediae and cercariae develop in the periesophageal lymphatic spaces the cercariae leave the snail and encyst in the skin beneath the scales and in the muscles of the fishes (the second intermediate hosts in the form of metacercariae or encysted cercariae The first larval stages (sporocysts rediae and cercariae) develop within several species of mollusks of the subfamily Bithyniinae (*Parafossarulus striatulus Bulimus fuchsiana, Bithynia longicornis, B. hafesi* and probably other related species such as *Melanoides tuberculata* (Gallard 1938) and *M. cancellata* Faust and Barlow 1924) which are the first intermediate hosts of the parasite Metacercariae are found in about 40 species of fresh water fishes of the families Cyprinidae Gobiidae Anabantidae and Salmonidae

In Canton the two species most massively infected are *Ctenopharyngodon idellus* and *Mylopharyngodon aethiops*, which are eaten raw In Peiping, in addition to the first species, *Culter aburnus* is the species which most frequently transmits the parasite

Definitive hosts are infested when they eat raw or poorly cooked fish containing the metacercariae or fish preserved in salt or vinegar In the intestine, the metacercaria sets free a young fluke which reaches the intrahepatic bile ducts and develops into the adult parasite in about 1 month The adult lays embryonated eggs which enter the duodenum in the bile, the eggs are passed with the feces, and a new cycle begins The entire cycle is completed in not less than 3 months

The number of parasites harbored may be quite large A case has been reported in which 21,000 specimens of the parasite were counted Kourí found 200 specimens in 1 patient and 20 to 50 specimens in others

This parasite may live many years in the biliary passages in man Two such cases have been reported in Panama One was a Chinese who had left China 25 years previously, the other patient had lived for 30 years in the Mauritius Islands Although both men had lived all this time far removed from endemic areas, living specimens were found at autopsy of the first man, and eggs were recovered from the stools of the second

PATHOLOGY AND HISTOLOGY

In mild clonorchiasis, the liver seems to undergo slight changes In cases of moderate or massive infestations, this organ increases in size The bile ducts become hypertrophied and dilated In old massive infestations, the organ may be greatly hypertrophied and occasionally shows whitish areas, which extend throughout the surface and represent cavities with fibrotic walls, derived from the hypertrophied, fibrotic, dilated bile ducts In some cases, carcinomatous transformations of the scirrus type, as Kourí has pointed out in 2 cases (Kourí and collaborators), are seen These also contain cavities with fibrotic walls filled with pus Occasionally the gall bladder is increased in size and contains dark, thick, and thready bile, with mucus, with one or more specimens of the parasite and many eggs On one occasion many vegetative forms and cysts of *Giardia intestinalis* were found with Clonorchis in the gall bladder In Kourí's experience, in a study of more than 60 cases of accidental death of Chinese residents in Cuba, about 25 per cent were affected with clonorchiasis in different degrees

The histologic lesions consist of inflammatory and hyperplastic reactions, which begin in the bile ducts recede, in cases of advanced massive infections, almost to the connective tissue, and occasionally to cells of the contiguous hepatic parenchyma In the walls of the duct, and surrounding it, infiltration of inflammatory cells is seen, with eosinophiles and lymphocytes predominating, and occasionally polymorphonuclear neutrophiles, causing a connective vascular tissue reaction with consecutive sclerosis of the walls of the bile ducts which in time become hypertrophied The epithelium of the biliary canaliculi undergoes mild hyperplasia and at times almost completely disappears, only rarely is this hyperplasia notable In such cases it leads to actual biliary adenomas, in a more advanced stage of the lesions, which is different from the pathology caused by *F hepatica*

In more advanced stages of the disease in cases of massive parasitism, the fibrous tissue invades larger areas of the parenchyma destroys the liver cells resulting in areas of necrosis and fatty degeneration of these cells In these cases one should study carefully the different portions of the liver because frequently when this stage is reached there are histologic and clinical signs in the liver due to malignant transformation (Kouri and collaborators) In severe and more advanced cases there is hypertrophic cirrhosis with symptoms of portal compression edema of the extremities ascites collateral venous circulation etc

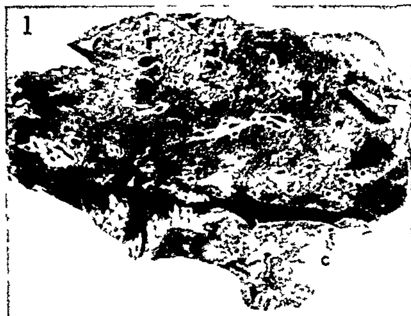


Fig 331 —Clonorchiasis hepatica liver This specimen contained severe lesions of clonorchiasis and carcinomatous transformation of biliary adenoma. *1* Surface of a section through the liver showing hypertrophic and sclerotic bile ducts with pericanalicular fibrosis *c* A large zone of carcinomatous sclerosis confirmed by microscopic examination. (Kouri Basnuevo and collaborators)

PATHOGENICITY

Clonorchis sinensis is the most frequent cause of distomiasis hepatica in human beings The disease is called clonorchiasis hepatica by *C sinensis* At times the clinical picture of the disease is quite grave with symptoms of gastrointestinal disorder anemia diarrhea ascites and edema of the lower extremities The development of the disease may be very slow If infestation is extensive patients may die in a state of cachexia

SYMPTOMS

The spoliative action of this parasite is of little importance but the mechanical and toxic actions and above all the irritative and inflammatory

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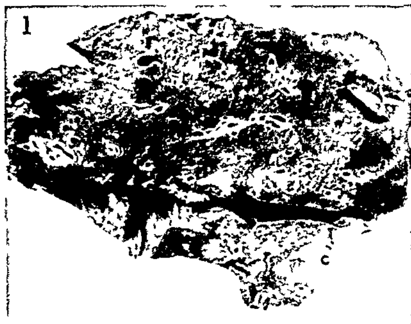


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Fig 332.—Clonorchiasis hepatica. *1*, Bile duct with 3 sections of the parasite in its lumen *2* Portion of *1*, higher magnification From left to right, *h*, hepatic parenchyma *c*, sclerotic wall of the bile duct with little if any epithelial hyperplasia, *g* and *p* body of the parasite *3* Another portion of the same bile duct showing *c* canalicular sclerosis *g*, slight epithelial hyperplasia with mild infiltration of leucocytes and *p* body of the parasite *4* to *10*, Microscopic appearance of different parts of the liver and ganglia from a case of clonorchiasis and carcinoma treated by Kourí and collaborators *4* and *5* Carcinomatous epithelial tubules and cords in the sclerotic tissue *6* and *7*, Ganglia of the hilum invaded by the carcinoma. *8* and *9* Zone of necrotic hepatic cells with sclerosis and infiltration of leucocytes in areas where carcinomatous areas are still scant. *10* Alveolar appearance caused by metastatic invasion of the carcinoma into the lymphatic sinuses of the ganglia (Kourí and collaborators)

actions provoked by the parasite are important in the production of hepatic lesions and the clinical picture of the disease

Fatty or fatty granular degeneration of the liver in the areas around the sclerosed bile ducts in cases of massive clonorchiasis is probably due to the toxic action of the parasite as well as to compression of the fibrous tissue on the hepatic cells Carrying of bacteria by Clonorchis in its migration from the intestines to the biliary and pancreatic ducts has not been completely studied

The irritative and inflammatory action of the parasite determines the tissue alterations in the affected organs in which more or less intense inflammatory and hyperplastic and occasionally neoplastic reactions are produced The intensity of these reactions varies with the intensity and duration of the infection Somatic alterations determine the symptoms which characterize the clinical picture of each particular case

When the number of distomes is considerable they may occasionally obliterate the bile ducts rarely the pancreatic duct causing retention of bile with resulting icterus although this seldom occurs

In cases of mild infestations individuals may show appreciable symptoms or symptoms may be very mild These mild symptoms frequently are not attributed to the parasite as in so many parasitic affections On the other hand in cases of moderate or massive infestation the symptoms are variable and the seriousness of the symptoms is in direct proportion to the number of parasites harbored The most frequent symptoms are gastrointestinal disorders greatly increased appetite alternating constipation and diarrhea sensation of heaviness and pain in the epigastrium and right hypochondrium and upon palpation enlargement of the liver In the more advanced stages continuous diarrhea may appear with bloody stools epistaxis icterus edema of the lower extremities and splenomegaly Reflex and toxic disorders may appear such as vomiting convulsions paralysis hemeralopia palpitation tachycardia vertigo and mental depression In the final stages of massive infestations the patients become anemic and cachectic before death

CLINICAL FORMS OF CLONORCHIASIS

Since these symptoms are not all present at the same time in the patient LeDantec has divided them into the following clinical forms

1 **Malignant or Pernicious Hepatic Colic**—This form begins abruptly as a hepatic colic attack The patient experiences violent pain in the right hypochondrium and in the epigastrium The pain is accompanied at first by vomiting of food later by vomiting of bile temperature is elevated icterus appears and the pulse is slow and thready After 2 or 3 days the fever is replaced by hypothermia and the patient falls into a coma With each attack the symptoms increase until eventual death occurs

2 **Peritoneal Form**—The patient shows tight abdomen diffuse pain upon pressure without regional localizations with tympanism muscle guard hiccups bradycardia or irregular pulse and vomiting

3 **Angiocholitic Form** —The dominant symptom is intermittent fever of irregular type not influenced by quinine A large and painful liver is found upon palpation The intermittent fever suggests malaria and the clonorchiasis hepatica may pass undiagnosed

4 **Acute Congestion of the Liver** —After many attacks of diarrhea the patient has a sensation of heaviness in the region of the liver substituted by moments of painful crises There is a subicteric cast The liver is enlarged and painful upon palpation

5 **Biliary Hemoglobinuric Form** —This form was described by Leray and Nogue and denied by Gaide Gaide estimated that there is no true relationship between the existence of the Clonorchis and the appearance of symptoms of hemoglobinuric biliary fever However when the individual harbors numerous trematodes the disease becomes worse and almost always terminates fatally

DIAGNOSIS

In cases of digestive and hepatic disturbances with or without fever and with eosinophilia one should always keep in mind the possibility of clonorchiasis if the patient comes from the Far East Symptoms or clinical pictures may simulate those of malaria biliseptic fever cholecystitis hepatic colic and jaundice The diagnosis must be verified by microscopic examination of the feces and of bile obtained by duodenal intubation

The eggs are very small and may easily escape detection in the stool especially in thick preparations Telemann s concentration method is excellent The technic described by Kouri for the parasitologic examination of bile in fascioliasis hepatica may also be used in the diagnosis of clonorchiasis

TREATMENT

The drug most commonly used in the treatment of clonorchiasis is gentian violet then sodium antimony tartrate

Malachite green Nile blue sulfate and gentian violet are given orally in 5 cg tablets 4 tablets daily before meals for 30 consecutive days According to Kawai the efficacy of this dye administered orally is in direct ratio to the doses administered and in inverse ratio to the number of harbored parasites In cases of recent infestation *the drug is usually curative* *In old* cases it reduces the number of parasites but does not lead to complete cure

The drug can also be used intravenously in the form indicated in the treatment of strongyloidiasis Reduction of the number of parasites in the bile ducts can also be attained by intravenous injections of the antimony salt solutions (Chattuck) particularly sodium antimony tartrate which is used also in the treatment of schistosomiasis On the other hand Otto and Chan Ching in 1935 seem to have had good results with the intravenous administration of gold salts

PROPHYLAXIS

The public should be warned against eating raw or incompletely cooked fish in endemic regions Although there are about 15 000 Chinese in Cuba 40

per cent of whom are parasitized by this worm, there is very little danger of spread of the disease because of the absence in that locality of the species of fish and snails which can act as intermediate hosts In addition to this, Cubans do not eat raw or incompletely cooked fish

It is difficult to control dissemination of the eggs in endemic areas because certain domestic and wild carnivorous animals act as agents of infestation To date, these agents have not appeared in Cuba despite the long period of time during which the Chinese have emigrated to Cuba and the high percentage of infected Chinese, who probably deposit the eggs of the parasite on the soil It may be that the eggs of the parasite are not viable in the dog

In clonorchiasis as well as in diphyllobothriasis sewage should not flow into rivers and lakes unless previously decanted filtered or disinfected, since, if this is not done snails and fishes which serve as intermediate hosts in the development of the parasite in endemic zones will be infested Ammonium sulfate has been recommended in endemic areas for disinfection of the excreta

For campaigns directed against mollusks drainage and the use of copper sulfate are suggested As with diphyllobothriasis, frozen or dried fish can probably carry the infection to other places from endemic areas (Binford)

2 OPISTHORCHIASIS

(Disease Caused by *Opisthorchis Felineus*, the Cat Liver Fluke)

HISTORY

The first human cases were reported in Tomsk Siberia, by Winogradoff in 1892

GEOGRAPHIC DISTRIBUTION

Opisthorchis felineus is found in dogs and cats in central and eastern Europe and in Siberia In the highly endemic regions of East Prussia Poland, and Siberia it is also found as a human parasite Cases have been reported in the Philippines, Japan, French Indo China, but it is not endemic in those regions where *C sinensis* abounds

CAUSATIVE AGENT

Opisthorchis Felineus (Rivolta 1884) Blanchard 1895

Synonyms—*Distoma conus* Gurlt 1831 *nec* Creplin 1825, *Distoma lanceolatum felis cati* von Siebold 1836 *Distoma felineum* Rivolta 1884, *Distoma lanceolatum canis familiaris* van Tright 1889, *Distoma sibiricum* Winogradoff 1892, *Distoma winogradoffi* Jaksch 1897, *Opisthorchis tenuicollis* (Rudolphi 1819) de Fejmont 1937

The *adult parasite* is lanceolate, the anterior extremity being narrow and the posterior extremity rounded It is 7 to 12 by 2 to 3 mm, and narrow The living specimens are reddish or reddish orange Spines are visible only in young, sexually immature specimens The ventral sucker is about 250 microns in diameter and is found in the anterior fifth of the body The oral sucker has the same dimensions as the ventral, it is subterminal and is directed toward the ventral surface

For further details see Gradwohl and Kouri (1948)

Eggs are ovoid, about 30 by 11 microns When the eggs are laid, the miracidia are completely developed

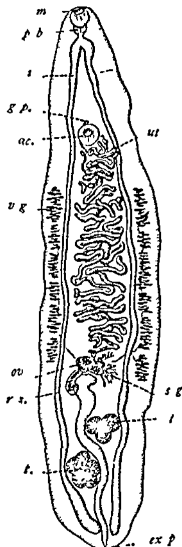


Fig 333—*Opisthorchis felineus* from a cat m mouth p b pharynx i gut g p genital pore ac ventral sucker ut uterus v g vitellarium ov ovary s g shell gland r s receptaculum seminis t testes ex p excretory pore (After Stiles and Hassall) (From *Fantham Stephens and Theobald The Animal Parasites of Man* Bale Sons and Danielson Ltd London)



Fig 334—Egg of *Opisthorchis felineus* (×1000)

Life Cycle

The miracidium does not leave the egg in the water The egg must be ingested by the intermediate host before this takes place The intermediate host is *Bul mus tentaculata* within which near the region of the rectum the sporocysts develop After 1 month the rediae leave the sporocysts and migrate toward the digestive gland where the cercariae are formed The cercariae leave the rediae before their complete development (Vogel) Approximately 2 months after the snail is infected the cercariae begin to leave These cercariae adhere to the scales of the second intermediate host the fish They lose their tails and penetrate into the muscles of the host encysting after 24 hours

According to Ciurea the following species of fish of the family Cyprinidae are parasitized in nature *Idus melanotus Tinca tinca Cyprinus carpio Barbus barbus Abramis brama Blicca bjorkna Leuciscus rutilus* and *Scardinius erythrophthalmus* The first 2 species are most frequently infected

The cercariae encysted in the muscles of the fish require about 6 weeks to mature When the definitive host ingests raw or partially cooked fish the metacercariae leave the cyst in the stomach of the host pass to the duodenum and go rapidly to the distal bile passages where they adhere to the biliary epithelium and grow to the adult stage in 3 to 4 weeks

Infection with *O felineus* is the result of eating raw or partially cooked fish infested with the metacercariae

PATHOLOGY, CLINICAL SYMPTOMS, AND TREATMENT

Pathology clinical symptoms and treatment are similar to those of clonorchiasis

PROPHYLAXIS

Prophylaxis consists in not eating raw or insufficiently cooked fish

3 Human Fascioliasis Hepatica

(Disease Caused by *Fasciola Hepatica* the Sheep Liver Fluke)

Synonyms —Sheep liver rot fascioliasis distomatosis hepatica

HISTORY

The first known parasitic trematode the *Fasciola hepatica* was discovered by Jehan de Brie in 13 9 In 1 60 Pallas found it in man for the first time In 1831 Kreplin discovered the miracidium In 1831 Leuckart and Thomas described the life cycle for the first time, in a digenetic trematode In July 1931 in Cuba Kouri Arenas and Basnuevo found the first autochthonous case of human distomatosis hepatica In May 1932 these authors reported their investigations in a monograph entitled La Distomatosis Hepática en Cuba submitting the first " cases in human beings as well as a description of the specific action of emetine in the treatment of this disease

There have been 100 cases reported in Cuba probably more than one third the total cases reported in medical literature which is approximately 100

GEOGRAPHIC DISTRIBUTION

This is a cosmopolitan parasite particularly abundant in those regions where domestic cattle and sheep are bred and where are found certain snails which serve as intermediate hosts

It has been found in America Puerto Rico Cuba Venezuela Argentina and Chile, in Europe Greece Corsica Italy Romania Hungary France U S S R and Scotland in Asia China Turkestan Syria Turkey, in Africa Algeria French Somaliland, in Australia Queensland In Cuba it is found in all the provinces but is more frequent in the west

CAUSATIVE AGENTS

Fascioliasis hepatica is caused principally by *Fasciola hepatica* and also by *F gigantica*

Fasciola Hepatica Linnaeus, 1758

Synonyms—*Distoma hepaticum* Linnaeus 1758, *Distomum hepaticum* Retzius 1786 *Planaria latiuscula* Goeze 1782 *Cladocoelium hepaticum* (Linnaeus 1758) Stossich 1892 *Fasciola californica* Sinitsin 1933 *Fasciola halli* Sinitsin 1933

Common Name—Babosa or duela del higado in Cuba, saguaype in Argentina, grande douve du foie in France, sheep liver fluke in English

F hepatica is quite common among cattle It has also been found in hogs and sheep Although there are no statistics regarding its distribution and frequency among the animals of Cuba, it seems to be more frequent in the western provinces, especially in Pinar del Rio



Fig 335—*Fasciola hepatica* Parasite stained with hematum eosin (*Original of Kouri and collaborators*)

Calvo Fonseca in 1943 reported that 61 93 per cent of the 549 cattle examined by Ricardo Perez, in the abattoir of Pinar del Rio, and coming from different counties of Pinar del Rio San Luis, San Juan, and Martinez, Vinales, Consolación del Norte, Consolación del Sur, and Guanajay, were parasitized by *F hepatica*, although in some districts the percentage was as high as 87 per cent in the cattle

F hepatica infestation has become a problem of major importance in Cuba during the last few years because of the increasing number of cases in human beings In 1931, Kouri and Arenas described the first 2 autochthonous cases To date, more than 100 cases in human beings have been reported in Cuba, the highest number on record, one third of the total cases reported throughout the world (Kouri, Basnuevo, et al, 1938)

The body of the parasite is flat and leaf shaped, varying in size, 2 to 3 by 1 to 1 5 cm It has at the anterior extremity a conical prolongation on the tip of which is found the oral sucker The ventral sucker lies behind the oral sucker It is larger than the oral sucker and

has a triangular opening the base of which lies toward the anterior end. The body of the parasite narrows gradually. The posterior end is blunt.

The first two thirds of the body has a whitish zone almost completely filled with the highly branched testes. With the exception of this latter zone the body of the parasite is gray, the color imparted by the vitelline glands. These glands are very numerous. At times the parasite is dark brown. This color is imparted by digested blood in the blind intestinal branches, which are very numerous throughout this region. The rosette-shaped uterus is filled with eggs. It is a distinct yellow mass contrasting with the clear zone described above. For further details see Gradwohl and Kouri (1948).

The *egg* of *F. hepatica* is one of the largest helminthic eggs of importance in medicine. It is oval, about 150 by 80 microns. It has a yellow covering or shell with a relatively small operculum. The contents consist of a fertilized ovule, often near one of the poles, surrounded by numerous polygonal vitelline cells.

Life Cycle

The eggs are excreted in the feces. In tropical countries they embryonate in the water in about 2 to 3 weeks at 25° C. Ciliated embryos which escape through the opercula swim freely in the water.

The first larval stage or miracidium was long thought to be one of the infusoria because of its ciliated epithelium. The larvae perish in 8 hours unless they enter an intermediate host. The larvae penetrate into the body of the snail and migrate toward the pulmonary tissue. Here they lose the ciliated epithelium, become spherical and develop into the sporocysts. The sporocysts contain numerous germinal cells which proliferate to form a third larval stage or redia. These rediae escape from the sporocysts and migrate toward the hepatopancreas of the snail where they continue their asexual metamorphosis by forming daughter rediae in summer and cercariae in winter.

Cercariae develop within the daughter rediae. The cercariae escape from the snail and swim about in the water for a brief period of time (8 hours), after which they lose their tail. They then encyst either freely in the water or attach themselves to aquatic plants. These are the metacercariae, the infesting larvae. If they are ingested by one of the definitive hosts of the parasite, they reach the intestine, their covering is dissolved, and each liberates a young or adolescent distome. These bore through the intestinal wall, reach the peritoneum, migrate toward the liver. Here they penetrate Glisson's capsule and the parenchyma of the liver and finally gain access to the bile ducts where they grow into adult forms in 3 months. The adult parasites lay eggs which enter the duodenum with the bile and eventually pass from the body with the feces, thus a new cycle begins. Occasionally, through the portal vein or the lymphatics, they enter the liver and right heart, thence the lungs and left ventricle to become erratically localized.

The intermediate hosts of *F. hepatica* are those gastropods with lungs and which belong to the genus Lymnaea, now divided into numerous subgenera. In Europe the intermediate host is *Lymnaea truncatula*, also found in Northern Africa and America. *L. cubensis*, which is found in Puerto Rico, Cuba, and Venezuela, and *L. mollis*, which is found in Puerto Rico. *L. viator* is found in Argentina. *L. bulimoides*, *L. columella*, *L. ferruginea* and others in North America. *L. pervia* and *L. japonica* in Japan. *L. acuminata* and *L. gedrosiana* in India. *L. ollula* and *L. rubella* in Hawaii. *L. swinhoei* in Formosa. *L. plicatula* in China. *L. brazieri* in Australia. *L. natalensis* in South Africa, and other species, as many as 21 in different parts of the world, belong ing to the subgenera Pseudosuccinea and Fossaria, and to the genera Bulinus, Galba, Succinea, Physopsis, etc. There is another gastropod, *Physa cubensis*, of very common occurrence in Cuba, which very probably is an intermediate host of *F. hepatica*.

PATHOLOGY

The liver of infested animals is hypertrophied and has thick fibrous cords of a white color in contrast to the reddish brown of the organ itself. These cords are usually found on the lower surface of the liver. They extend

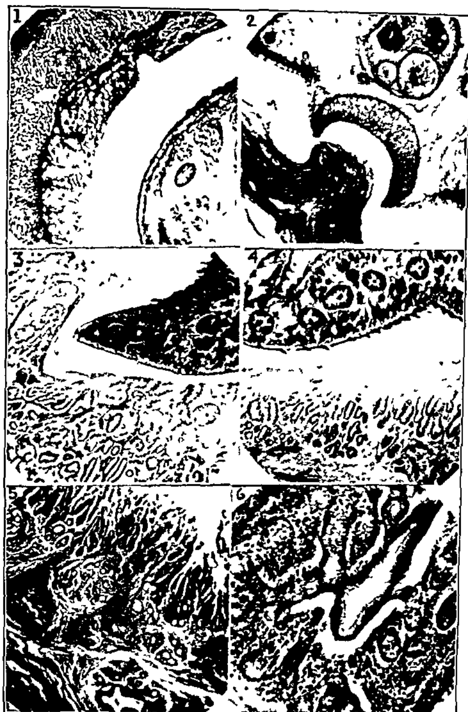


Fig 336—*Fasciola hepatica* Hepatic lesions in beef *1* Part of hypertrophied and ... vessels containing distomes *From left to right* hepatic lobules, parasite *2* *From below upward* part of vein tissue ... distome cirrus sac and contents (seminal vesicle ...) *3* and *4* Portions of hypertrophied bile duct hyperplasia of the canalicular epithelium and a dissection of the parasite adenomatous hyperplasia of points of contact with the parasite infiltration with eosinophiles *5* and *6* Adenomatous epithelial hyper... hocytes and eosinophiles (After Kouri and Arenas)

superficially underneath the fibrous capsule and then penetrate into the parenchyma of the organ These cords represent hypertrophied and sclerotic bile ducts

In macroscopic sections the lumina of these ducts are constricted some times to a very great extent and contain a dark substance consisting of mucoid pus eggs the parasite and its feces In old and massive infestations the sandy concretions are in the form of black calcareous tubes which cover the inner surface of the hypertrophied bile ducts When these old infestations particularly in sheep are of a massive character one may also see large convoluted cavities with thick fibrous walls These cavities are formed by intercommunication of large bile ducts which become sclerotic and dilated subsequent to peripheral blockage The bile ducts have fibrous walls The markedly hyperplastic epithelium takes on an adenoma like formation the corium is infiltrated with cells of inflammation among which many eosinophiles and lymphocytes are present

In massively infected animals the hepatic lesions may lead to hypertrophic cirrhosis portal compression with ascites etc

In addition to hepatic invasion subcutaneous and muscle abscesses produced by the parasite as well as lung ocular cerebral and other localizations were observed in Cuba

Eosinophilic febrile symptoms were observed by Kouri and collaborators in cases showing high eosinophile counts painful liver enlargements and often symptoms considered as acute abdominal conditions as well as transitory lung infiltrations in which *F hepatica* was discovered

Buccopharyngeal fascioliasis pharyngeal lesions have been observed in human beings these were caused by the irritative action of young trematodes

SYMPTOMS

The symptoms will be described with reference to infestation of human beings observed by Kouri et al in Cuba Some patients may not show any symptoms or may show very mild symptoms of gastrointestinal character while others may present more or less serious clinical pictures During the period of invasion there are fever eosinophilia acute abdominal symptoms and hepatitis The eggs of the parasite do not appear for about 3 months The majority of the patients studied by Kouri and his collaborators gave a prolonged history of gastrointestinal hepatobiliary nervous and general disorders—symptoms which were old and refractory to treatment and had not been associated previously with this disease The real cause of this disease remained unknown for a long time until the parasite was discovered in the patient

The gastrointestinal symptoms consist essentially of gastric dyspepsia functional disorders of the colon with alternate constipation and diarrhea

Hepatobiliary symptoms are characterized by pain in the region of the liver and gall bladder repeated hepatic colic with or without jaundice Fever may be present There are chronic cases interrupted by recurrent acute crises

with septic symptoms with eosinophilia and leucocytosis and *intermittent* apyrexia or slight rise in temperature usually in the evening. The nervous system is sometimes affected. Kouri and Valverde observed a case in which the patient had epileptiform spells. In another case observed by Kouri, Anido and Silveira, the digestive disturbances drove the patient, a woman, into an unbalanced mental and nervous state.

In massive infestations the general status of the host is eventually affected: the patient loses weight, becomes weak and finally anemic. Eosinophilia usually accompanies the anemic condition even during the acute septic crisis of the disease. With recurrence of every acute septic crisis there are high fever, marked leucocytosis, usually with eosinophilia and polynucleosis, the intensity of which varies inversely with that of the eosinophilia.

Cases of fascioliasis hepatica infestation observed by Kouri and his *collaborators had been tentatively diagnosed before discovering their parasitic* nature as follows: cholecystitis, hepatic colic, obstructive jaundice, appendicular colic, duodenal ulcers, bilioseptic fever, acute amebic hepatitis, acute abdomen, and malaria.

DIAGNOSIS

*One should always think of F. hepatica as a possible cause of gastrointes*tinal or hepatobiliary disturbances which may or may not affect the general status of the organism, of nervous or mental disorders, and of relapsing septic *crisis with a previous history of digestive or hepatic disorders.* This is especially true if eosinophilia is present with septic pictures, with high fever and leucocytosis. One can determine by laboratory investigation whether the cause of the disease is parasitic or not.

For technic refer to Chapter 72.

Eosinophilia is frequent. Intradermal, precipitin and complement fixation tests are indirect methods which may be of some value in the diagnosis. The antigen used consists of extracts of *F. hepatica*.

Flocculation tests for the diagnosis of syphilis, particularly the Meinicke and Kahn, usually give false positive results in fascioliasis hepatica. These reactions become negative after treatment with emetine.

If it is not possible to perform these laboratory tests, the therapeutic test is used. Administer emetine hydrochloride, which will not only cure the *patient, but will also establish the fact that the disease is due to* infestation with *F. hepatica*. This drug is specific for *F. hepatica*, as well as for *Endamoeba histolytica* (Kouri, Arenas and Basnuevo).

TREATMENT

Bacigalupo of Buenos Aires, with Bengolea and Velazco Suarez, reported for the first time in 1930 a human case of fascioliasis hepatica which had been cured with emetine hydrochloride. Kouri states: "We can affirm categorically that the problem of cure of this disease has been solved since we discovered (1931) and later demonstrated (1932) the high fasciolicidal



Fig. 33.—*Fasciola hepatica* eggs in human bile obtained by duodenal intubation. *1*, Eggs with transverse folds caused by pressure of the cover glass as the specimen dries. *2*, Egg with elevated operculum and granular protoplasm. *3*, Egg with spherical refractive cells and slightly separated operculum in freshly removed bile. *4*, Typical eggs in human bile. *5* to *8*, Eggs in various stages of atrophy and degeneration as a result of small doses of emetine hydrochloride, a powerful fasciolicide. (Original photomicrographs of Kouri, Basnuevo and Arenas.)

action of emetine hydrochloride if given in small doses the total dose is 0 5 *centigram per kilogram of body weight* for adults in consecutive daily injections of 4 centigrams each by intramuscular route This completely and definitively cures the disease (Kouri Arenas and Basnuevo 1931 1932)

Very few cases of apparent failure by this drug in human fasciolasis hepatica have been reported These failures *were usually due to the fact that* the treatment was not properly controlled or unfertilized eggs of Ascaris had been erroneously mistaken for eggs of *F hepatica*

Another possible source of error which can be corrected if biliary control is followed is mistaking the eggs of this parasite for those of *Fasciolopsis buski* in endemic areas

Lievre in 1934 prescribed intravenous injections of 1 per cent Magdala rose in human fascioliasis hepatica

PROPHYLAXIS

From a study of the life cycle of this parasite one may work out individual and general prophylactic measures against the disease The most frequent habitual definitive hosts in Cuba are beef sheep and hogs It has been recently found that rabbits are naturally infected in Cuba General prophylactic measures directed against dissemination of the eggs of the parasite are consequently quite difficult As general measures we recommend a campaign against the intermediate host through physical or chemical means *(desiccation drainage and copper sulfate solutions)* These precautions may effectively decrease the number of snails

In general the trematodes as well as Diphyllobothrium have as first and only intermediate hosts fresh water invertebrates mollusks for trematodes and crustaceans for Diphyllobothrium General prophylactic measures for both groups consist in preventing sewage from flowing into rivers and lakes without previous purification or chemical destruction of the eggs using ammonium or copper sulfate

Individual measures are 1 Avoidance of eating raw vegetables coming from infested areas The most frequently contaminated vegetables are *lettuce* and water cress especially the latter because it grows in water These two vegetables are usually eaten raw in salads 2 Since water might contain metacercariae it should always be filtered or boiled

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CHAPTER 44

FASCIOLIASIS HEPATICA IN CHILDREN

ANTONIO SELLEK

Fascioliasis hepatica is frequently found in cattle sheep goats and hogs See Chapter 43

The disease is extremely rare in children only 3 cases having been reported in the entire world in the past 20 years One of these cases was observed at the Municipal Children s Hospital in Havana by Vazquez Fausa Sellek Inclan and Garcia Vázquez (1943) during 200 000 coprologic examinations on 150 000 children Carani (1936) and Burgi (1938) saw the disease *in a 4 year old boy and Garcia Hernandez (Matanzas Cuba 1946) reported* the disease in an adolescent

The adult parasite eggs and life cycle are described in Chapter 43 and will not be repeated here

SYMPTOMATOLOGY

There are no recognizably specific symptomatic manifestations of infestation by *Fasciola hepatica* because the symptoms are variable Localization of the flukes in the gall bladder and ducts causes hepatic lesions by mechanical effect hepatitis and cholecystitis secondary bacterial infection and even cirrhosis Syndromes which may be manifest are hepatic and biliary colic epigastric pain acute febrile icterus and pseudotyphoidal forms—loss in weight dyspepsia and intestinal disturbances such as diarrhea alternating with constipation—and even appendicitis

The clinical manifestations of the disease are often confused with other pathologic processes Reports are found in the literature of surgical treatment because of erroneous diagnosis also calculous cholecystitis as a result of conditions due to distomes has been found at operation the flukes being rolled into a ball in the gall bladder and ducts

LABORATORY DIAGNOSIS

Most authors note that diagnosis is made by finding a few eggs in the fecal material and a large quantity of eggs in the bile The ordinary enrichment methods give rather mediocre or even negative results Best results are obtained by centrifuging diluted excreta or by letting the material sediment in a conical glass tube

Blood eosinophilia especially the persistent form is considered of great importance in diagnosis When septic complications are present polynucleosis and leucocytosis are found and the eosinophiles generally do not decrease

This fact is of considerable clinical value in considering the possible existence of the disease With a decided febrile setting eosinophilias of 15 35 and 40 per cent have been observed

Cutaneous allergic tests as well as complement fixation tests in infection by *Fasciola hepatica* have been of some use in differentiating the disease

Attention has been called to the possible positivity of the flocculation test for syphilis (Kahn Meinicke) This test is positive before treatment with emetine is begun later returning to normal and becoming negative after completion of treatment We have not been able to confirm these observations Because of this we suspect in these cases a possible coexisting syphilis which might have been reactivated perhaps by infestation with *F hepatica*

TREATMENT

Of the numerous medicaments proposed for treatment of human distomatosis by *F hepatica* all have been found wanting except emetine hydrochloride the heroic drug in these cases The action of emetine hydrochloride upon human infestation by *F hepatica* is remarkable To Kouri and his school is due the credit for indicating its exact precise and typical action

In one of the author s cases reported with Vazquez Pausa Inclan and Garcia Vazquez (1943) of a 9 year old boy weighing 19 kilograms accustomed to eating raw lettuce and water cress cure was effected by using a dose of 2 centigrams of emetine daily for 6 days then the same dose every other day 6 more times A total of 24 centigrams was injected Eighteen days after termination of the treatment biliary intubation and examination of the feces were carried out Absence of eggs of *F hepatica* was noted in both examinations The digestive disturbance which had been characterized by constipation and diarrhea disappeared Eight months after treatment examination of the bile was negative The result of treatment in this case was a rapid definitive cure which has persisted to the present time

In the case reported by Garcia Hernandez (Ceiba Mocha Matanzas 1946) a 14 year old adolescent weighing 65 pounds results were obtained by use of intramuscular injections of a total of 21 centigrams of emetine hydrochloride in daily doses of 3 centigrams

PROPHYLAXIS

See Chapter 43 for a discussion of prophylaxis in fascioliasis hepatica

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CHAPTER 45

SCHISTOSOMIASIS JAPONICA

FREDERIK B BANG

INTRODUCTION

Schistosomiasis japonica or infection by the trematode *Schistosoma japonicum*, is an extremely common disease in a large circumscribed area of the Orient The economic effect of this preventable infestation in endemic areas is incalculable and it represents one of the chief causes of mortality in all age groups in these areas Exact figures are impossible to obtain but in moderately endemic areas (Kofu Japan) as much as 5 per cent of the total population may be under treatment during the year In hyperendemic areas such as that on Leyte Philippine Islands approximately 10 per cent of the children have well developed cirrhosis and about 80 per cent have hard en larged livers

It has been recognized as a disease entity in Japan for some time and has been called *Katayama disease* after the name of a prefecture where it was particularly prevalent The worm itself was first recovered from a human autopsy by Fujinami in 1904

LIFE CYCLE OF SCHISTOSOMA JAPONICUM

Schistosoma japonicum is parasitic in a great many mammals including man It inhabits particularly the mesenteric blood vessels The mature males measure 5 to 26 mm by about 0 5 mm in diameter the females are sometimes shorter than the male later longer (Cort 1921) The female has 100 to 200 eggs in the uterus at one time and these are laid in batches of 10 to 100 in the intestinal wall of the host particularly in the submucosa and the mucosa By means of destructive secretions the eggs work their way through to the lumen where they are discharged with the feces frequently in a blob of bloody mucus During transit through the mucosa the egg develops into a mature miracidium which hatches from its shell and swims free after coming in contact with water This miracidium gains entrance into an intermediate host a small snail within 24 hours or dies

After a period of development of 5 to 7 weeks in the snail cercariae burst from a sporocyst which has developed in the snail s liver and swim free in the water This stage is infectious for almost all if not all mammals and in most of them is capable of develop ing through the full cycle Dogs cats also pigs horses and sheep are all capable of car rying the worm and excreting the eggs

During penetration of the skin the cercariae lose their tails change their shapes and disappear into the systemic circulation In experimental infections of the rabbit large numbers may be found in the lungs on the second and third day and appear in the mesen teric vessels and liver on the third day They mature and mate in the small hepatic radicles and in about 4 weeks migrate to the smaller veins draining the large and small in testine and appendix (Faust and Meleney 1924) Here they remain for an unknown period of years depositing eggs in batches in the submucosa and mucosa and perhaps also directly into the blood stream whence they are swept to the liver



Fig 338 Adult male and female *Schistosoma japonica* (Courtesy of Army Medical Museum)

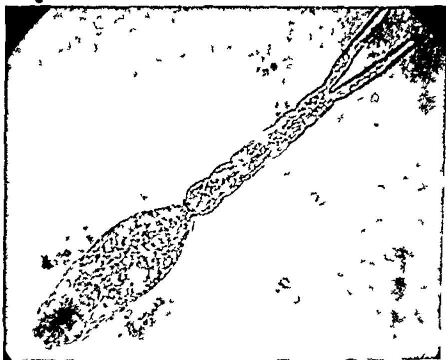


Fig 339 —Cercaria of *Schistosoma japonica* (Courtesy of Army Medical Museum.)

Aberrant worms have been found in the right auricle of the heart and in the inferior vena cava in experimental infections (Africa and Garcia, 1941 Krakower, Hoffman, Axt mayer, 1943), and such deviations are a likely explanation of the anomalous localizations of eggs in the brain and skin of man

Intermediate Host

S japonicum must spend a portion of its life resident in a small snail of the genus Oncomelania The distribution of the 4 species of this snail, *O quadrasi* in the Philippine Islands, *O formosana* in Formosa *O nosophora* in Japan and China and *O hupensis* in China, appears to explain the distribution of the disease in the Orient The intermediate host is unknown in the Celebes This snail may easily be confused with snails incapable of carrying the disease, and identification should be confirmed by an expert

Failure to find the host in small areas does not mean that transmission does not occur there, careful search along river banks has sometimes failed to yield the snail, yet epidemiologic evidence has clearly shown that infection took place in the river The presence of infection in snails is easily determined by crushing them in clean water and examining them with a dissecting microscope Typical forked tailed cercariae may be found either within the sporocyst in the liver or swimming free in the water These should not be confused with other trematode larvae, and careful comparison with known specimens or textbook pictures should be made

PATHOLOGY

The eggs deposited in the tissues are the principal cause of the pathologic changes Adult worms living free in the blood vessels provoke little tissue or cellular reaction The recent demonstration by Vogel (1942) that the eggs have a relatively short life span (3 weeks), after which they degenerate or calcify, has made the pathogenesis of this infection more understandable Unfortunately, much of our knowledge is derived from experimental infections, but with this as a background a fairly complete picture may be outlined The natural disease may be divided roughly into 3 stages (1) an incubation period of about 4 weeks, which corresponds to the development of the adult worm and its early migration (2) the allergic or acute phase, and (3) the chronic stage which may or may not be symptomatic

The Incubation Stage

The first stage, that of *invasion and maturation of the parasite,* is the least well understood According to Faust and Meleney (1924), heavy cercarial infection of a dog was accompanied 15 hours later by innumerable red slightly raised, pin point sized spots all over the portions of the body which had been immersed Serial sections showed cercariae in the corium surrounded by a slight tissue reaction consisting of edema, a moderately dense accumulation of wandering cells mononuclear cells, and neutrophilic and eosinophilic polymorphonuclears It is likely that such changes are slight or absent in the human being, for very few skin rashes or symptoms of itching were reported in the acute infections in the Philippine Islands

Lesions produced during migration of the parasite are minimal but distinct They consist chiefly of hemorrhages caused by mechanical blocking of the capillaries In the lungs they are visible as early as 24 hours after exposure and persist as late as the tenth day On microscopic examination many young

forms of *S japonicum* are found in the arterioles and capillaries and a few free in the alveolar spaces There may also be a perivascular accumulation of polymorphonuclears chiefly eosinophiles Maturation of the worms occurs in the portal system and is unaccompanied by pathologic change except when infection is so dense that mechanical blocking of circulation may produce necrosis of the liver cells (Faust and Meleney 1924) Although so called toxic effects on the kidney have also been described in massive experimental infections such effects in the average human case are doubtful

The Acute or Allergic Stage

The beginning of egg deposit marks the close of the usually asymptomatic incubation period ' and the beginning of the acute disease The actual mechanism of egg deposit in *S japonicum* seems to differ from that of the 2 other schistosome infections of man In contrast to *S mansoni* and *S haematobium* the female *S japonicum* contains at one time 100 to 200 eggs in utero and deposits them in batches of 10 to 100 Eggs all of one stage of development are found together within the capillaries and venules of the submucosa

Development of the egg may be divided roughly into 3 stages knowledge of which is basic to understanding the pathology These stages are more fully described in the section on laboratory findings but may be outlined here The immature or undeveloped egg which is deposited in the tissues develops within 10 days into the mature egg containing a motile miracidium This egg in turn lives another 7 to 10 days and then dies The degenerating form may either calcify or gradually disintegrate It is difficult to differentiate the reaction of the host to the immature and mature egg Reaction to the degenerate egg soon changes from an acute inflammatory to a chronic phagocytic foreign body reaction

Grossly the distinctive feature of the acute reaction is the presence of scattered pinhead sized firm abscesses which are chiefly found in the submucosa and muscularis of the intestine and throughout the liver tissue In animals killed within a few days after the first eggs have been found in the feces these changes may be just beginning If the infection is heavy nodules are also found in the lungs Lobular pneumonia has been described in such lungs but in these cases it is difficult to separate the effect of the concomitant treatment Microscopically the immediate response around freshly deposited eggs is an intense cellular infiltration of lymphocytes and polymorphonuclear leucocytes mostly eosinophiles These develop into tiny necrotic abscesses Later fibroblasts and multinucleated giant cells may enter the picture Contiguous lesions may coalesce forming undermining ulcers in the intestine Older lesions become more granulomatous and with the appearance of an increasing number of fibroblasts and giant cells pseudotubercles are formed After the miracidium dies most of the cells may disappear leaving a small fibrosed nodule in the center of which remains a distorted shrunken egg Kupffer cells scattered throughout the liver may contain hematin but such cells are usually concentrated near the areas of egg deposit This pigment histologically identical with malarial pigment is also found in mesenteric

lymph nodes and in the spleen The eggs are frequently found in the mesenteric lymph nodes and the lungs and occasional anomalous ones are deposited in the brain and skin Those eggs which are deposited in the mucosa or submucosa of the gut work their way after some days into the lumen or the tiny abscess described above may rupture and drain into the lumen The time necessary for the eggs to reach the lumen accounts for the fact that newly laid eggs are rarely found in the feces Breaking off of pieces of mucosa and the rupture of abscesses accounts for the presence of blobs of bloody mucus containing masses of eggs

Each of the 3 fatal acute cases on Leyte showed characteristic yellowish miliary lesions in the large and small intestine and liver a monocytic lobular pneumonia varying in extent infiltrated with eosinophiles with eggs scattered throughout the lungs (Thomas Bracken and Bang 1946)

The Chronic Stage

After some weeks of fever the acute symptoms of the disease disappear and the physical aspects become more vague This transition to the chronic stage is not well understood and our ideas are confused by observations made in hyperendemic areas where residents are subject to continued heavy exposure The picture is further confused by the fact that the duration of the natural infection is unknown estimates varying from 2½ years to life It is likely that immunity or at least a heightened phagocytic response to the eggs develops in the chronic cases The fact that populations exist and multiply in these hyperendemic areas where almost all are infected is evidence enough of an acquired tolerance Adults show a much smaller proportion of enlarged livers than children (Bang Hairston Graham and Ferguson 1946)

Experimental light infections of monkeys studied at autopsy 4 to 6 months after infection fail to show the acute allergic aspect—necrotic abscesses with heavy infiltrations of eosinophiles—but show only minimal lesions in the intestine and a slaty discoloration of the liver This is not due to any peculiarity of the infection in the monkey for the yellow pinhead abscesses are clearly present in the acute phase even with infections of 5 to 10 pairs of worms (Bang—unpublished studies)

The pathology of the chronic disease then may be discussed with the understanding that this is not a necessary sequence to the acute disease It is probable that the chronic cases seen in hospitals are results of repeated heavy infections Reported autopsies of cases have been too few in number to describe the distribution of lesions and on this point one must be particularly cautious in transferring the results of animal studies to the human being In infections of the dog chronic granulomatous ulcers are found in both large and small intestines but are most common in the large The intestinal wall is usually thickened by scar tissue According to Faust and Meleney (1924) the lesions in the human colon became more common toward the rectum Externally the omentum may be matted together and adherent to the intestine Thickening of the intestinal wall may be great enough to form a solid tube

Round solid masses may extend on to the peritoneal surface These are fibrous nodules with necrotic areas and pigmented spots from which eggs may be obtained

Internally the mucosa loses its regular arrangement, "and now presents an uneven surface on which are all grades of papillary projections of the epithelium from minute spots barely raised above the surface to broad, firm slightly raised masses and pedunculated papillomata perhaps a centimeter in length There may be minute points of hemorrhage where eggs or abscesses are breaking through to the surface" (Faust and Meleney, 1924)

Microscopically the most marked change is the massive increase in fibrous tissue involving all layers but most marked in the submucosa "Eggs are present as before in all layers of the wall often in large groups Some are still immature and seem never to have produced a reaction in the surrounding tissue Others are in the midst of their activity and are surrounded by polymorphonuclear leucocytes Still others have been caught in the scar tissue and have either become calcified or are surrounded by foreign body giant cells Some have even been invaded by giant cells which often occupy the egg shell as the miracidium formerly did and may be mistaken for it" (Faust and Meleney 1924)

Eggs may be found singly or in groups in the thickened mesentery The presence of eggs in the mesenteric lymph glands makes it likely that the lymphatics leading from the intestine may carry eggs from the submucosa and be surrounded by scar tissue on the way

Thrombi of the mesenteric veins are particularly common in experimental infections of the guinea pig (Bang and Hairston, 1946) The larger vessels of the human being are less subject to blocking but with masses of worms crawling and twisting around each other like the strands of a rope, thrombi are likely to develop The main portal vein itself and the large branches in the liver are particularly liable The part played by this fact in the development of the enlarged spleens of chronic cases is unknown

Little has been added to our knowledge of the pathology of the chronic disease since Faust and Meleney, and thus they will be extensively quoted

Liver —

This organ often presents a most extraordinary picture which adequately explains its part in the production of the late symptoms of the disease In size it may be considerably enlarged or slightly shrunken In our 3 cases the liver weighed 1 943 1 485 and 1 490 grams respectively It is characteristic to find a hard irregular projection of the left lobe extending below the costal arch in the midline The organ is irregular in shape *presenting nodular swellings ranging up to 3 cm* in diameter and deep fissures and scars often extending 1 cm into its substance The left lobe is often proportionately larger than the right although the hyperplasia of new liver tissue may make it appear normal in some places The capsule may be diffusely thickened into a white fibrous coat or the thickening may be limited to small areas *In one of our cases the entire exterior of the organ* was gray and fibrous with many pock like depressions in the thickened capsule There are usually fibrous tags on the surface representing old adhesions to the parietal peritoneum or adjacent intestines The ligaments are often thickened particularly the *falciform* liga

ment which may contain enlarged vei[illegible] [illegible] drainage The gall bladder wall may be thickened due to its close asso[illegible] [illegible] capsule of the liver and perhaps to the deposit of eggs in its wall

The cut surface of the liver vare[illegible] [illegible] with the intensity and duration of the disease In mild cases it may [illegible] [illegible] few small scars usually near the surface of the organ In more severe [illegible] [illegible] a diffuse increase of fibrous tissue somewhat coarser in distribution than [illegible] [illegible] hobnail liver of nodular cirrhosis Normal or fatty liver tissue bet[illegible] the [illegible] strands suggests the persistence of considerable functional capacity in th[illegible] [illegible] cases show massive destruction of liver tissue with replacement by scars

Histologically the liver in hu[illegible] all stages of the process of reaction to the eggs of the parasite The pre[illegible] [illegible] s that of repair with the replacement of polynuclear leucocytes [illegible] with the production of masses of scar tissue which may or may not be a[illegible] recognizable portal spaces In the scar tissue are eggs often in large numbers A[illegible] the intestine the tubercle formation may be definite and the eggs may be surr[illegible] [illegible] invaded by foreign body giant cells Hematin deposit is more marked than in experimental dogs The Kupffer cells often stand out as black masses Phagocytic cells in portal spaces are laden with small or large granules In the 'tubercles' especially at their periphery such pigment laden cells are often numerous The liver cells themselves may be relatively normal in appearance or they may show all degrees of fatty infiltration This change is not at all proportional to the degree of infection and is probably only secondarily associated with the parasitic infection Intense scarring of the organ may produce localized areas of typical chronic passive congestion or of obstruction of bile capillaries The liver capsule shows thickening by fibrous tissue in which may be many lymphocytes or other wandering cells and occasionally large veins representing a collateral circulation

Spleen —Faust and Meleney point out the inverse relationship between the size of the liver and spleen in their autopsies This is borne out by surveys of children in hyperendemic areas where enlarged spleens are found in only a small percentage of cases—and these late in their course—while the typical hard enlarged livers are commonplace Macroscopically the spleen is hard and has a thickened capsule and firm surface when cut Microscopic sections show the fibrous tissue basis of these changes—thickening of the trabeculae and infiltration of the reticulum The association of a hard enlarged spleen cirrhosis of the liver and anemia in the chronic progressive cases has frequently led to the confusion of these cases with Banti's syndrome (Campbell 1936), which in itself is not a clinical or etiologic entity It has so far not been possible to reproduce this syndrome in animals by infection with the schistosomes presumably because a more extensive anastomosis of veins prevents the increase in portal venous pressure present in human cases (Krakower, Hoffman and Axtmayer 1943)

Lungs —In contrast to the acute infections gross or microscopic lesions are uncommon Eggs however are frequently found on section These may have either broken through the abscesses in the liver to enter the hepatic vein and thence the heart and lungs or have gained the same end by passage through anastomoses in the hemorrhoidal region The presence of eggs in the **heart** itself is similarly explained

Lesions of the **brain** have been recognized for many years as being due to collections of eggs and are most likely due to anomalous localization of the

worms A case report from the Philippines tells of finding eggs in the lun brain kidneys and heart with pseudotubercle formation in the myocardi (Africa and Santa Cruz 1939) The remarkable thing is not the presence these unusual lesions but rather the fact that the worms are so highly spec that the vast majority of them migrate to the mesenteric veins

SYMPTOMS

The acute disease may vary from a severe intermittent febrile illness w frequent abdominal cramps but little diarrhea to asymptomatic infecti The chronic disease is characterized chiefly by diarrhea or dysentery a enlargement and often subsequent shrinkage of the liver with chronic asci and emaciation

The first symptom a transient itching caused by schistosomes in ma results from the penetration of the skin by the cercariae and occurs at the mo in 10 per cent of cases It is of little diagnostic significance as there is nothi typical about it

Incubation

There follows a latent or incubation period which corresponds to t period of development of the worm to maturity and egg laying Clinical this period may be defined as the time interval between exposure and the fir definite symptoms In most cases it has been difficult to fix this time interv because of the continued exposure The outbreak of the disease during tl reoccupation of Leyte Philippine Islands in 1944 gave rise to more exact da of this nature In a study of 73 cases Billings et al (1946) found an averag incubation period of about 40 days with a minimum of 25 days and a maximu of 78 days In 12 cases where there was only a single exposure—swimming an infested river—there was an average incubation period of 42 days minimum of 26 and a maximum of 58 As will be brought out in the sectio on laboratory diagnosis this corresponds closely to experimental studies c light infections of monkeys and dogs

The brevity and mildness of the symptoms of urticaria headache dia rhea and fever during this period make it difficult to know whether the symptoms are related to the behavior of the worm or not

The Acute Disease

All gradations of severity occur During the outbreak on Leyte wher there were about 1 500 cases they ranged from subclinical cases discovere by surveys of heavily exposed units to severe febrile cases in which death oc curred within 2 months of the onset In about 1 500 cases or more there wer 3 deaths (Thomas Bracken and Bang 1946)

The onset of the acute symptoms may be abrupt with headache malaise chills feverishness a nonproductive hacking cough anorexia generalize aches abdominal cramps and right upper quadrant pain Less frequentl seen are urticaria of varying severity backache and diarrhea or constipation

Nervousness may be marked Weight loss is extreme in cases of some weeks' duration The stool is usually normal in appearance flecks of bloody mucus on the surface of the stool are occasionally seen

The course of the acute disease varies with the severity which in turn is probably related to the intensity of the infection Fever may last from 1 to 8 weeks Particularly striking is the remittent saw tooth type of curve with a peak in the afternoon and a return to normal by morning This afternoon peak is often accompanied by accentuated symptoms and may well be related to activity of the miracidium within the eggs This would correspond to the cyclic behavior of the microfilaria in filariasis

The urticaria may range from small fleeting wheals to giant patches of indolent edema which do not completely respond to Adrenalin These allergic aspects of the acute disease were responsible for the early descriptive name *urticarial fever* which was so well described by Lambert (1910) as follows

"This eruption, unlike that of most pyrexial states is of an urticarial type It appears on any part of the body as a small wheal which rapidly assumes a large size attaining frequently 3 inches to 4 inches or more in diameter These wheals are firm white and raised from the surface feeling to the touch like a solid oedema and having frequently a central pinkish area of congestion and a well marked areola They remain out' for an hour or two, continuing to spread As they disappear the central part first resumes the normal skin appearance and areola fading last of all so that on examination of the patient, one finds the patches in all stages of development from the early wheal as large as a sixpence to sinuous raised red lines the outlines of former areas some of which measure several inches in circumference

' The eruption may continue to appear and fade away and reappear for a week or more *It leaves no mark nor trace behind it and does not avoid parts of the body that it* previously favoured The patient may be practically free from it for many hours when it again makes its appearance with renewed vigour The irritability of the rash varies considerably, but taken generally is not so annoying as that of simple urticaria It is frequently noticed that when the rash is well out the patient feels better, although there may be be no remission of his fever at night Dermatographic wheals can be elicited in many cases

' The temperature is normal or but slightly raised in the mornings It commences to rise about noon and reaches its height which is seldom above 102° F about six in the evening from thence gradually falling to normal its decrudescence being accompanied usually with sweating The presence or absence of the rash has no effect upon the temperature, *which may continue for days after all signs of the former have disappeared*

"The urticarial rash frequently appears on the mucous membrane of the buccal cavity and also on that of the nose in the latter position causing temporary impediment to the respiration through the nostrils the blockage passing off to the accompaniment of a profuse discharge of watery fluid The larynx may also share in the transient oedema but never so far as is known to a dangerous extent the slight embarrassment to respiration *caused by the swollen mucosa soon passing off*

A common and almost diagnostic symptom seen in Billings (1946) cases was a peculiar stiffness of the neck About $^2/_3$ of these patients complained of pain on motion either rotation or flexion, with soreness of the sternocleidomastoid and trapezius muscles The stiffness lasted from 24 hours to 2 weeks Cramping pains in the upper abdomen without diarrhea are common In severe cases the patient may be prostrate and semicomatose with a high spiking fever

PHYSICAL FINDINGS

In the acute stage of the disease physical findings are not remarkable enlargement and tenderness of the liver is the most common and is often accompanied by epigastric tenderness. The spleen may or may not be enlarged. The significance of splenic enlargement in troops is hard to evaluate because of the high incidence of malaria suppressed by Atabrine (Johnson and Berry 1945).

As a transient finding scattered pulmonary infiltrations may be demonstrated by x ray (these may become extensive enough to give a miliary type of seeding) but most cases show nothing at all.

Sigmoidoscopy in about 2/3 of the acute cases reveals scattered small yellowish papules in the mucosa or submucosa. They are firm about 2 mm in size. Biopsy or scraping shows them to be tubercle like abscesses containing eggs (Johnson and Berry 1945).

Unusual Cases

The incidence of neurologic signs and symptoms among acute cases seems to be something under 2 per cent. The clinical picture in the early part of the disease consists chiefly of paralysis and drowsiness followed by coma and incontinence. Weakness spasticity exaggerated deep reflexes a positive Hoffman or Babinski indicate pyramidal tract involvement. These signs usually improve under treatment as the temperature reaches normal (Carroll 1946). Probably a variety of other symptoms occur depending on the location of the eggs in the brain. We may assume that they came there by the arterial circulation or were deposited by a pair of worms residing in the sinuses of the brain but worms have not been recovered in this location in human autopsies. Cases have been reported in which symptoms resembling acute encephalitis have been followed by hemiplegia (Carroll 1946).

Recently a case of papular eruption of the skin in the region of the eighth intercostal nerve has been clearly established as due to deposits of eggs in this area (Fishbon 1946).

Relapses

Relapses are worth special mention because it should be well recognized that *following a course of treatment with an antimony drug eggs may reap*pear in the stool—without the development of any of the original symptoms. This is the rule rather than the exception. Such a renewal of egg laying on the part of the adult worm may as in the acute cases cause egg deposit in the brain so that the first symptoms *in some cases are those of a gradually* developing tumor of the brain.

Chronic Disease

*As emphasized in the section on pathology the acute infection is not neces*sarily followed by the chronic disease. Indeed there are few if any cases recorded where this has occurred and where reinfection has been ruled out. Many cases are supposed to recover spontaneously. Chronic disease the so called *third stage is the picture seen particularly in hyperendemic areas where*

continual reinfection is common In this stage wasting and lassitude set in the appetite is poor and there are attacks of dysentery with pain and tenesmus at stool and minor attacks of fever Nosebleeds are common in children The liver enlarges and becomes very hard with a sharp irregular edge it is particularly palpable in the midline The spleen later enlarges descending as far as halfway between the umbilicus and the pubis It is hard and not tender These symptoms gradually increase until ascites sets in—then generalized anasarca Severe anemia is common Many cases in the terminal stages show severe jaundice Carcinoma of the liver often occurs in the chronic stage but since exact statistics are not available it is not known how frequently it is a cause of jaundice



Fig 340—Chronic case of schistosomiasis in Philippines. (Courtesy of O H Graham)

IMMUNITY

True immunity has now been demonstrated to exist in a number of helminthic infections It is thus to be expected that it would play some role in this disease Some mechanism for acquiring resistance or tolerance in hyperendemic areas must exist or the population could not survive That this is related to real immunity is made likely by the reduced incidence of positive stools in adults (Ferguson Graham Bang and Hairston 1946) and by the lower percentage of enlarged livers in the adults

In the pig and carabao a similar lowered incidence of positive stools was noted in the older animals Experimental work by Fujinami (1916) showed

that a horse which had been heavily infected and recovered was apparently immune to reinfection The test exposure produced an overwhelming infection in 2 control horses

LABORATORY FINDINGS

As the demonstration of eggs in the stool of a suspected case is the only sure method of diagnosis, the characteristics of the eggs will be *discussed* first Vogel (1942) divided the life period of the egg into 3 different periods the immature, the mature, and the degenerate

Diagnosis of either acute or chronic disease should be based on the presence of mature eggs (Hairston, 1945) Attempted diagnosis based on immature or degenerate eggs often leads to error, and once a false positive diagnosis has been made and treatment started, subsequent failure to find eggs does not disprove the diagnosis



Fig 341 —*Schistosoma japonicum* eggs in intestine (Courtesy of Oscar Felsenfeld.)

The Mature Egg —The mature egg is usually but not always yellowish in color and discoid oval in shape They are usually larger than the common helminth eggs (ascaris, hookworm, etc), varying from a minimum of 55 to 65 microns in length in young eggs to a maximum of 85 to 90 microns in mature eggs The shell may be covered with varying amounts of detritus but is never completely obscured Although a spine is almost always present in newly laid or immature eggs, it is usually difficult to demonstrate it in the mature egg The characteristic feature of the schistosome egg is the miracidium contained within A good rule to follow is to call an object a schistosome egg only when both the outline of the shell and the embryo can be seen If the miracidium is alive, some of the following movements can be seen (1) muscular twisting and jerking of the whole or parts of the miracidium (2) ciliary action particularly around the mouth but also all around the sides, and (3) the beating of the flame cells Once recognized as mature living schistosome eggs, it is very hard to mistake them for anything else

The Immature Egg —The immature egg is given no diagnostic significance in this discussion because (1) It has often been the basis of incorrect diagnosis when confused with unfertilized ascaris eggs or even plant cells (2) Although it is the first type of egg to appear free in the stool in hyperinfected animals, studies of light infections have failed

to show that it appears significantly in advance of the mature eggs (Hairston and Bang unpublished) There are occasional cases reported in which immature eggs only were found for some days before the appearance of mature eggs (Billings, Winkenwerder, and Hunninen, 1946) but confirmed cases are rare (3) Heavily infected individuals with severe acute symptoms have such a typical clinical history and course that a diagnosis can be made clinically, and, if necessary treatment can be started immediately Laboratory findings can subsequently verify the diagnosis

Although atypical eggs should not be the basis of a diagnosis they are of considerable importance in following the activity of the adult worms, particularly during treatment (Bang and Hairston 1946)

The newly laid egg is clearly separated from the other immature eggs by the presence of large vacuoles in the yolk which obscure the oocyte This stage is very rarely seen in the feces If found it would indicate that the eggs had traversed little tissue before entering the lumen and might thus indicate ulceration

The young immature egg is darker than the mature and lacks the vacuoles of the newly laid egg The embryo is seen as a clear area in the middle of the ovum This stage may be confused with the decorticated unfertilized egg of ascaris but may usually be differentiated by the fact that these ascaris eggs are smaller, lack a clear central area, and contain larger granules As it grows older, the embryo takes up a larger portion of the available space, so that a stage before organization may be recognized The embryo lacks the clear cut outline of the developing miracidium but most of the yolk has disappeared and the shell is filled by a blastula like embryo The presence of the immature egg in the stool is of significance in treatment for it means that oviposition has occured within 10 days to 2 weeks The disappearance of immature eggs from the stool is evidence of response to treatment (Bang and Hairston, 1946)

The Degenerate Egg—The mature egg which has been described lives about ten days, and then if it is still caught within the tissues the miracidium first loses its motility, then tends to shrink to one side and the whole egg becomes black in color Finally the outlines of the miracidium completely disappear leaving blackish refractile areas within Oil drops and plant cells may mimic this last stage of disintegration which is too poorly defined to be identified with certainty The presence of degenerate eggs in the stool is obviously of entirely different significance from that of immature ones Degenerate eggs may continue to appear in the stool as long as 3 weeks after successful treatment has been begun Hatched miracidia and shells from eggs may also be found (Faust, 1946)

First Appearance of Eggs

Eggs may be demonstrated in the stool shortly after the onset of the acute symptoms According to our experience they may be found in light experimental infections about 5 weeks after exposure In acute moderately severe human infections they have usually been found in the first few examinations Chronic severe cases have in the past often failed to show eggs It is likely, however, that recent methods (Faust and Ingalls, 1946, Loughlin and Stoll 1946) of concentrating the eggs will eliminate this difficulty

Method of Examination of Stool

The schistosome eggs are deposited in batches in the mucosa of the large intestine, often in the sigmoid colon Thus the stool has, to a great extent been formed by the time the eggs, often contained within a patch of mucus, gain entrance into the lumen of the bowel The whole stool should be taken to the laboratory and pieces of mucus searched by direct examination Only if this fails should a concentration method be used

For details of examination see Chapter 72

The detection of schistosome eggs in the stool by the hatching technic has a limited value since only live mature eggs may be detected this way (Faust and Ingalls 1946 Hairston 1945) The technic is based on the fact that the miracidia when in water of the proper pH hatch and swim to the surface

If a sample of feces is diluted in water about 1 part of feces to 20 or more parts of water *placed in a bottle with a stopper in which a glass tube has been inserted* the tube filled with water and the whole left overnight at room temperature miracidia may frequently be found swimming at the top of the water in the tube They may be seen with the aid of an ordinary hand lens The temperature should be between 28° and 33° C. to obtain best hatching (Magath and Mathieson 1946)

Blood Picture

Eosinophilia—Acute schistosomiasis japonica is characterized by an extreme and progressive eosinophilia so that as many as 9 to 95 per cent of the leucocytes (but averaging about 50 per cent) may be eosinophiles The total leucocyte count may vary from 9 000 to 30 000 of which the eosinophiles comprise 6 to 95 per cent Thus the eosinophilia does not necessarily account for the entire rise in the leucocyte count There seems to be little correlation between the severity of the disease and the degree of eosinophilia

Anemia in the course of the acute disease is unusual in well nourished *people but common in chronic severe cases Its causal relationship is unknown* since these cases usually have a multitude of other parasites as well as deficiencies in diet Heavy infections with *S japonicum* however may well *cause anemia since the worms continually ingest red blood cells and convert them* to hematin The cirrhosis of the late stages of the disease is another cause of anemia

Eosinophilia decreases in the chronic disease so that in the presence of the many other parasites usually found in patients in endemic areas it loses all diagnostic significance

Skin Tests and Complement Fixation

Most of the immunologic tests for the presence of schistosomes have been *done on other species than S japonicum but since none of the tests differentiate* between the various species we may utilize some of the conclusions Antigens are of 2 types (1) saline extracts of adult worms and (2) alcoholic extracts of the hepatopancreatic glands of infected snails *(Fairley* 1926 Minning 1941) The latter is difficult to prepare in quantity if working in *japonica* territory since the snail host Oncomelania is so small but large quantities of the former may be prepared from a *freshly killed and exsanguinated* dog or young pig The skin test is of the immediate type and is read in 15 minutes to half an hour Delayed reactions occur only rarely In *S mansoni* the Fairley complement *fixation test becomes positive* late *in* the stage of invasion and by the time eggs are found in the stool 97 per cent of the cases are positive Chronic cases are usually positive A similar situation seems to obtain in early *S japonicum infections* (Katzin and Most 1946)

Practical Value in Schistosomiasis Japonica—The claim has been made that there are cases of infestation by *S japonicum* in which eggs are not found in the stool Immunologic methods would be of value in determining the presence or absence of infection Such claims will have to be re evaluated in the light of recent methods of concentration of the eggs particularly since one pair of *S japonicum* lays such large numbers of eggs

The value of the test in following the effect of treatment may however be another problem for it is now well recognized that although the eggs may disappear from the stool the worms may survive and later reinitiate egg laying Furthermore the female worm seems to be more susceptible to treatment so that many cases may carry residual infections of males after treatment In diagnosis however there is no practical substitute for the finding of typical eggs nor, after treatment for the *continued* absence of eggs

TREATMENT

Drugs of the trivalent antimony series have found widespread use since the introduction of tartar emetic and later Fuadin in the treatment of *S haematobium* in Egypt Accurate comparisons of the relative efficacy of the many antimony compounds now available have not been made Such comparisons are particularly difficult because it has been shown clinically and experimentally that larger amounts can be given and can be continued or not over a longer period of time with a higher percentage of cures (Pillings Winkenwerder and Hunninen 1946 Mason Daniels Paddock and Gordon 1946)

Most clinicians prefer to use *tartar emetic* (antimony and potassium tartrate) in the acute stage It is given in a concentration of 0 5 per cent Solutions should be freshly prepared preferably in 5 per cent glucose in physiologic saline or in isotonic sodium chloride The solution should be perfectly clear and free of sediment It may be made by adding sterile powdered drug to the saline using sterile instruments or may be sterilized after preparation by boiling gently for 5 minutes It should not be autoclaved The drug is best tolerated several hours after a light meal Treatment of adults is usually begun with 0 04 Gm tartrate (8 c c of a 0 5 per cent solution) and then if no reaction has occurred increased doses are given on alternate days until 0 14 Gm (28 c c) is given in 1 dose A total of 15 doses is given in this way until 360 c c have been administered Since tartar emetic corrodes the tissues it is important to keep the needle within the vein Toxic effects include coughing immediately upon injection nausea vomiting stiffness of joints a sense of constriction of the chest pain in the upper abdomen dizziness and collapse There may be transient electrocardiographic changes without clinical signs Children are given roughly 1/3 to 1/2 the above dosage

Since recent pharmacologic studies have clearly shown that antimony drugs are cumulative in the body (Brady et al 1945) the treatment should not be repeated for several weeks As both blood and tissue levels of antimony rise rather slowly under the regime outlined above it would seem logical

to start with large doses and then after saturating the body taper off or stop treatment This has been done in the treatment of chronic cases of *S haematobium* and *S mansoni* (Alves and Blair 1946) but until careful studies are made of *S japonicum* infections it cannot be recommended as a routine

Fuadin has the great advantage of ease of administration It was formerly given in gradually increasing doses until 40 c c had been administered but this is now recognized as inadequate and a course of 70 to 80 c c is considered standard for the average adult The solution is injected intramuscularly preferably in the gluteus away from nerves The first 3 doses of 1 5 c c 3 5 c c and 5 0 c c are given on successive days On the fifth and subsequent alternate days 5 c c are given until a total of 16 doses has been given provided no toxic effect has appeared Nausea and vomiting may not be an indication to stop treatment if mild but if severe treatment should be suspended temporarily or the amount of drug injected should be reduced Children should be treated with a comparable dose by weight

Anthiomaline has no known superiority over the 2 drugs here recommended and is not infrequently painful *Emetine* (the active principle of Ipecac) has been used extensively in the treatment of chronic cases Its relative value has not been established and until it has this drug cannot be recommended in preference to those of known value

A review of the treatment of chronic cases has emphasized the value of potassium antimony tartrate (Li and Thompson 1934)

Response to Treatment

In the acute stage of the disease response to treatment is disappointingly slow It may even appear that the disease is progressing despite treatment or often it is obvious that the downward course of fever and improvement have begun before treatment began It is however possible to demonstrate that treatment has a definite effect for Billings et al (1946) found that fever and severe symptoms tended to disappear on an average of 2 weeks after treatment was initiated *regardless* of the duration of the illness preceding treatment The delay in response is accounted for by a series of interrelated facts The disease symptoms are caused chiefly by the eggs in the tissues These are not susceptible to the action of the drug but as Vogel has shown they have a sharply limited life span of about 10 days from deposit of the eggs to maturity and perhaps another 10 days until the death of the miracidium within the egg It can be shown that antimony treatment inhibits egg production by the female worm thus cutting off the supply of pathogenic eggs Those that have been laid however mature normally and their presence continues to stimulate fever and symptoms until they die Another fact that must not be overlooked is that though egg deposit does not stop for some years the acute allergic phase of urticarial fever' is usually spontaneously cured some weeks after the initiation of symptoms—this without treatment

Consideration of treatment should be divided into 2 phases (1) the primary effect on the disease at hand—the recovery from fever malaise and cramping and (2) the final effect on the worms—the prevention of relapses

The first effect of antimony treatment is to drive the worms from the small branches of the mesentery to the liver Then the reproductive system is affected so that the ovary and vitelline glands of the female degenerate and oviposition ceases With this comes a general shrinking of the worm and a loss of hematin Unless treatment is continued beyond this stage the worm may recover the ovaries and vitelline glands regain their shapes and functions and the pair return to their location in the branches of the mesenteric veins This is the explanation of the relapses so called laboratory relapses because they frequently have few symptoms after the allergic phase has passed

It is well therefore to treat severe acute cases a little longer than the average case so that complete killing of the worms may take place Specific treatment of chronic cases has been in the past a routine and wholesale procedure It has not been possible to give the general supportive treatment needed in severe anemia extensive cirrhosis and generalized anasarca Particularly in these latter types has treatment been continued only as long as symptoms are present Treatment in every case that can tolerate it should consist of the full course outlined above and accordingly an individual should not be considered cured unless he fails to relapse in 2 years A relapse is defined merely as the reappearance of eggs in the stool

A word of warning on the increased amount of antimony which is being used to produce a higher percentage of cures is issued by Lippincott Paddock Rhees Hesselbrock and Ellerbrook (1946) who found that hepatic function was abnormal in a large number of American soldiers who had been treated with both tartar emetic and Fuadin Liver function as determined by bromsulfalein retention and serum bilirubin gradually returned toward normal after cessation of treatment

EPIDEMIOLOGY AND PROPHYLAXIS

Acute single infections which were brought to the clinician s attention prior to World War II were limited chiefly to 3 classes of individuals sportsmen who had waded through infected rice fields and water children who had waded had swum or had fished in infected water and sailors on warships who had washed or swum in shallow rivers while at anchor These people were usually foreign to the endemic zone and their exposures furnished clues as to the areas in which infection was taking place On this basis it was assumed that deep quiet waters were relatively free of infection (Faust and Meleney 1924) Sea water undiluted by fresh river water is safe since cercariae are unable to survive in it (Ingalls 1946)

The outbreak of acute infections in the troops on Leyte emphasized the part played by the muddy shallow rivers which drain an infected area Infection was highest among troops whose occupation forced them to enter streams (bridge builders) and among those who deliberately exposed themselves by swimming in these streams The incidence of infection was low in the men who during the fighting waded fully clothed through rice fields

in endemic areas (Sullivan and Ferguson, 1946) Furthermore, transmission of the disease ceased when exposure to these rivers was stopped It is likely that considerable protection was afforded to the fighting men by the clothing they wore, for though different cloths vary (roughly with the fineness of the weave) *in their ability to keep cercariae out*, common weaves like cotton khaki and O D woolen cloth prevent the penetration of many cercariae (Ferguson, Graham, Bang, *and Hairston*, 1946)

The visitor to an endemic area should, therefore, stay out of all infected water, if forced to wade through flooded fields or ditches tightly woven clothing impregnated with benzyl benzoate or dibutyl phthalate will give considerable protection Dibutyl phthalate or even dimethyl phthalate, commonly contained in the recent mosquito repellents, when smeared on the surface of the skin, will protect against infection for an hour or so and through occasional light rinsings These measures are not a substitute for *avoidance of exposure* Drinking water should be chlorinated to give at least 1 part per mil*lion residual chlorine at ½ hour Shower water is safe after chlorination or* after standing for 2 days Studies of potential hosts of *S japonicum* in this country have emphasized the improbability of introduction into the Americas (Stunkard 1946)

The spread of the disease within an infected community and the control of this spread is an entirely different problem from that of the prevention of infection in the occasional visitor Here the snail host, the reservoir host including man, and man's chief occupation in such areas (rice farming) make a cycle of transmission of the worm from one host to another such a tightly *welded chain that it has been difficult to break it Elimination of* the disease is theoretically possible in a number of ways

Elimination of the Snail—At present there are available no chemicals of sufficient selective toxicity and low cost that they could be spread throughout an area and eliminate the snail In many places the area occupied by the snails is so great, the value of the land so low, and the density of the population so relatively low that this approach is not economically sensible It has been of value, however in small highly populated areas of Japan A considerable decrease in the infection has been obtained by burning along infected irrigation ditches with flame throwers or by cooking with live steam (Miyajima 1939), or by spreading lime or calcium cyanamide as an accessory *fertilizer* Recent studies indicate that the dicyclohexylamine salt of dinitro ortho cyclo hexylphenol is the best available snailicide (McMullen and Graham, 1947), and that Paris green applied at a rate of 250 pounds per acre is also effective, *but no compound tested was found of practical value in large scale* control of Oncomelania

Theoretically it would be possible to prevent infection of human beings by preventing exposure, but if the planting of the seed beds of rice and the plowing of the rice fields are periods of greatest exposure, it is impossible to prevent it Most of the inhabitants of these areas are furthermore *unable* to afford clothing which would be protective

In many cases man is the chief reservoir of infection Thus it would be theoretically possible to prevent the spread and continued existence of the disease if human feces were both efficiently and sanitarily used The collection of night soil and its use as a fertilizer has therefore received considerable attention and it has been demonstrated that if the feces stand for several days in the collecting pits before distribution to the field all of the miracidia die and the snails do not become infected Furthermore if the fields are fertilized during the dry season infection again does not take place The inevitable human breaks in this technic however have been sufficient to prevent its being successful so far In other areas moreover cattle pigs and sheep serve as reservoir hosts and thus make control difficult if not impossible

A comparison of the casual chance scattering of human feces in the Philippines with an ordered disposal of them as seen in the use of night soil in Japan makes it clear that it is not merely the use of human feces as fertilizer which is responsible for the maintenance of the disease but rather the general level of sanitation which maintains the disease in areas where the snail host is present Night soil which is carefully collected and cured in pits and finally spread on dry soil has little chance to spread the infection but continual soil pollution by human feces may raise the percentage of infected snails to 20 or 30 per cent

Mass treatment of infected individuals is of little over all value for failures of cure and incomplete treatments when combined with the inability of such programs to get all of the infected individuals under treatment are sufficient to maintain disease transmission on a high level

Future work must then be directed to obtaining an efficient chemical which in low concentrations can selectively kill snails

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CHAPTER 46

SCHISTOSOMIASIS HAEMATOBIA AND SCHISTOSOMIASIS INTERCALATA

CLEMENT CLAPTON CHESTERMAN

SCHISTOSOMIASIS HAEMATOBIA

Synonyms.—Endemic hematuria, genitourinary schistosomiasis or bilharziasis

DEFINITION

Schistosomiasis haematobia is a chronic endemic disease manifesting itself mainly in hematuria and associated disorders of the urinary organs but occasionally affecting the rectum, the appendix, the lungs and other organs due to infestation of the pelvic veins by *Schistosoma haematobium* and the irritative effects of their eggs which escape in urine and feces.

HISTORY

In 1851 Bilharz, assistant professor at the Cairo School of Medicine, wrote to Siebold in Germany that he had discovered the *Distoma haematobium* in the mesenteric veins of a native Egyptian. He was soon able to show that the terminal spined eggs were the cause of the endemic hematuria in the Nile Delta, a disease which had existed from time immemorial as proved by the discovery of eggs in the desiccated organs of mummies. Bilharz considered that the lateral spined eggs more frequently found in the feces were distorted forms from the same parasite, which was named by Cobbold in 1859 *Bilharzia haematobia*. The generic term *Schistosoma*, previously used by Weinland in 1858, has priority, however.

Harley (1864) observed that lateral spined eggs were never found in Natal and concluded that the local blood flukes must be a different species which he named *Bilharzia capensis*. When Manson in 1902 saw a patient from the West Indies with exclusively lateral spined eggs in the feces he postulated the existence of two distinct species, one shedding lateral and the other terminal spined eggs. Sambon confirmed this hypothesis on epidemiologic grounds in Egypt in 1907 and proposed the name *Schistosoma mansoni* in appreciation of this one of his many generalizations. Looss strenuously contested the dual theory, even though Turner in Nyasaland had noted that female worms laying lateral spined eggs were exclusively found in the embrace of males with 9 testes instead of the usual 4 recognized in the male *S. haematobium*.

It was left to Leiper in 1915-1918 to demonstrate the morphologic, epidemiologic and clinical differences between the two species.

GEOGRAPHIC DISTRIBUTION

Egypt and the Nile Valley, North East and West Africa, the Congo, Central and South Africa, Madagascar, Mauritius, Reunion; small endemic foci in Portugal and Southern Greece and Cyprus, Israel, Iraq, and Iran.

THE CAUSAL AGENT

Schistosoma Haematobium (Bilharz, 1852) Weinland, 1858

Synonyms—*Distoma haematobium* Bilharz, 1852, *Gynaecophorus haematobius* (Bilharz 1852) Dies, 1858, *Bilharzia haematobia* (Bilharz, 1852) Cobbold, 1859, *Bilharzia magna* Cobbold, 1859 *Thecosoma haematobium* (Bilharz, 1852) Moquin Tandon, 1860, *Bilharzia capensis* Harley, 1864, *Bilharzia aegyptiaca* Miyagawa, 1924

Schistosoma haematobium is one of the digenetic trematodes or flukes, the paired worms may survive for as long as 30 years in the mesenteric or vesical veins of man, their usual definitive host They can also develop in many laboratory animals, guinea pigs, rats, and mice and can infect hedgehogs monkeys, and sheep

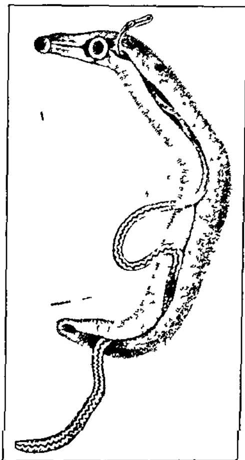


Fig 342—Adult *Schistosoma haematobium* Male carrying female in the gynecophoric canal (After Looss) (From Fantham Stephens and Theobald The Animal Parasites of Man, Bale Sons and Danielsson Ltd, London)

The *male* measures 10 to 15 mm long The flattened posterior 4/5 of its body has folded over edges which make it appear as a round worm about 1 mm thick In the groove so formed (gynecophoric canal), the female passes her adult life, and there is some evidence that the male is monogamic In the cylindrical anterior end is a small oral sucker, and just caudal to it a large ventral sucker or acetabulum The whole body is covered with small cuticular tuberculations

The 4 (or 5) *testes are situated dorsally and just caudal to the ventral sucker* and their vasa efferentia open by a single vas deferens in the genital pore situated on the ventral surface

The female is larger (20 to 28 mm) thread like (0.25 mm), and darker in color from contained blood. Its small skin bosses are confined to either end which lie outside the gynecophoric canal. The 2 suckers are smaller and less muscular and just behind the ventral one opens the vagina. This leads to the uterus which occupies most of the anterior ⅔ of the body. In the mature worm it may contain anywhere from 30 to 100 eggs in varying phases of development. The ovary and the shell glands (vitellaria) lie posteriorly and their ducts (oviduct and vitelline duct) at their common junction with the uterus are surrounded by the ootype where the eggs are fertilized and receive their shell.

In *both sexes* the alimentary canal starts at the oral sucker and divides near the ventral sucker, with which it is unconnected, to reunite again to form the blind cecum which runs the length of the posterior half of the worm.

Life Cycle

The mature worms lie coupled in the smallest pelvic veins capable of accommodating them, and the female, either still embraced by or temporarily advancing from her male partner, lays her eggs one by one, spine last, in the smaller venules of the vesical or mesenteric plexuses. How the eggs advance against the blood stream to reach the mucosa of the bladder or bowel is not entirely understood. In the mucosa the contained larva or miracidium secretes a lytic substance which helps the egg to dissolve a path toward the lumen and escape in urine or feces.



Fig. 343.—Eggs of *Schistosoma haematobium* in urinary deposit, photographed by dark ground illumination. (Photomicrograph by D. M. Blair, published by permission of F. Goodliffe, Southern Rhodesian Public Relations Department.)

The egg is oval, tapering to a pointed spine at one end, blunt at the other. Its average measurements are 150 by 60 microns, though there may be considerable variations. By osmosis through the permeable shell, the egg swells and bursts when shed into water and liberates the free swimming larva or miracidium.

The miracidium can remain alive in the egg in moist feces or sterile alkaline urine for some weeks, but in water it survives for about 24 hours. By means of its cilia it swims actively, and if the appropriate snail is available it will burrow its way into its tentacles to reach the liver. In this organ, which becomes a yellowish orange color visible through the shell of the infected snail, the double development into a thin walled sporocyst and daughter sporocysts takes place.

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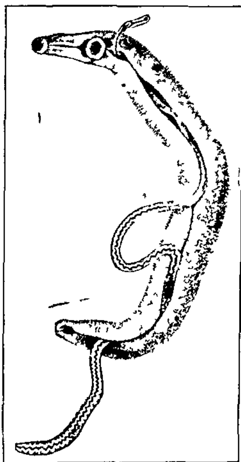


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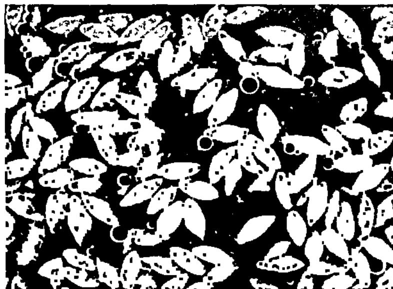


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After 4 to 8 weeks as many as 300,000 forked tailed cercariae, all of one sex, develop from one single miracidium These are discharged between the snail's body and shell, in swarms, for periods varying from 10 to 75 days

As numerous miracidia can penetrate and develop in one snail, the daily output of cercariae may be very great They are just visible to the naked eye and can be seen swimming tail first toward the surface of a vessel, and then sinking again They can survive for 5 or 6 days but are infective only up to 3 days Being unable to feed they must find a human host or perish



Fig 344 —Schistosome cercariae photographed by darkground illumination (Photographs by D M Blair published by permission of F Goodliffe Southern Rhodesian Public Relations Department)

The Vector

Various species of very similar thin walled sinistral snails act as the intermediate host in different parts of the endemic areas

In Egypt and Palestine *Bulinus truncatus* with its variants *B contortus, B dybowski B innesi* are the hosts, in East Africa and Mauritius, *B forskali*, in West Africa *Physopsis globosa*, in Congo and Natal *P africana*, while in Tunis it is *B brochi* The European vector is a flat snail *Planorbis dufouri* found in South Portugal and in Morocco Species of Melania, *M nodocincta* and *M tuberculata*, have been suspected in Nyasaland

PATHOLOGY

The life cycle is completed in man who suffers according to the number of cercariae which successfully penetrate his skin and survive to mature in his

pelvic veins The drying of cercaria infected water on the skin combined with the prodding action of the anterior sucker aided by a lytic ferment enable the cercariae to penetrate the intact integument leaving their tails behind them

Cercariae can of course equally well penetrate the mucous membrane of the mouth pharynx and esophagus if infected water is drunk or used for oral hygiene A valuable amount of skin irritation but little cellular reaction results and the metacercariae (or schistosomulae) reach and enter small veins leaving little trace of their skin passage except it be a few small petechiae Carried to the lungs they remain there only sufficiently long to squeeze through the capillaries in order to reach the pulmonary veins Some may escape during the process by capillary rupture but there is no evidence of asthma or pneumonitis at this stage though there may be a transient urticarial rash

Only those which happen to leave the aorta by the celiac axis or mesenteric arteries and then reach the liver via the portal vein are destined to survive All others are destroyed in whatever tissue they reach without causing symptoms

Liver

The second and third weeks are passed in the liver in the small intrahepatic branches of the portal veins The products of metabolism of the growing worms produce acute inflammatory reaction and swelling of the whole organ which is noticeably tender in heavy infections

Migration of the adolescent male and female worms now occurs and with unerring accuracy they creep aided by their rough skin bosses against the portal blood flow to reach their chosen habitat This migration is rendered easier by the absence of valves in the tributaries of the portal veins but why the inferior mesenteric vein should be invariably selected is still obscure The worms proceed to its terminal tributary the superior rectal (superior hemorrhoidal) vein which has its origin in the rectal plexus This plexus communicates freely with the vesical plexus in both sexes with the prostatic plexus in the male and the uterovaginal plexus in the female The worms once located in these small veins will mature and pair off in another few weeks and in from 10 to 12 weeks after entry into the human host oviposition commences

Bladder

Most eggs are laid in the venules of the vesical plexus and dissolve their way to the submucosa of the urinary bladder Causing at first only a slight hyperemia in the overlying mucosa they tend as numbers increase to aggravate in groups which raise small yellowish discrete tubercles or grains Infiltr
raised
and as
organ which becomes markedly thickened A roughening and puckering of the mucosa results with papillomatous outgrowths on the ridges and gravel

and phosphatic calculi in the pouches. The deposit of eggs sometimes becomes calcified and grates on the knife edge when cut.

Fibrosis may involve the ureteral orifices causing stricture, stenosis and hydronephrosis with resulting complications. The urethral opening is apt to be narrowed by inflammation and partially occluded by debris. Secondary infection usually complicates the picture, leading to perineal abscess and urinary fistulas.

Finally, new growths may develop, bilharzial carcinoma of the bladder being common in Egypt even in young adults.



Fig. 345.—Radiograph of genito-urinary system after Uroselectan. Shows small calcified bladder, dilated ureters and right pelvis. (Photograph supplied by R. Coleman.)

Pelvic Organs

As the vesical veins become occluded or insufficient for the process of oviposition, neighboring veins may be involved and extension of infiltration and fibrosis take place in the vesiculae seminales, prostate, penis, male and female urethra, vagina, uterus, broad ligaments, Fallopian tubes and even the ovaries. The rectum is, however, generally the first overflow site, but eggs are rarely

found higher up in the large bowel Infiltration of the appendix without acute inflammation is however not infrequent in Egypt and West Africa (Lovett Campbell 1948)

Pulmonary Lesions

Eggs of *S haematobium* are more often found in the lungs than those of *S mansoni* because the possibility of embolism from pelvic veins is greater They cause obstruction of the small arterioles and pass through their walls to

Fig 216 S[illegible] 30 years of age An angiomat[illegible] of cavernous type

provoke the characteristic tissue response outside them, ending in fibrosis and small nodular scars More serious arterial lesions are probably the result of the presence of paired worms in the arterioles The numbers of eggs thus laid *in situ cause necrosis of the vessel walls and* consequent dilatation or sclerosis of the pulmonary artery itself Parenchymatous changes are less common, and eggs are very rarely found in the sputum Asthma, chronic bronchitis, emphysema, and fibrosis are results of pulmonary bilharziasis and lead to chronic right heart failure



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Ectopic Lesions

Faust (1948) has recently defined these ectopic lesions as local reactions to the worms and their eggs, occurring outside the portal caval venous circulation, including the extension of the latter to the pulmonary arterioles

The ectopic sites in which eggs of *S haematobium* have occasionally been found are conjunctiva, skin, spinal cord brain and heart As has been noted *above, overflow phenomena from choked pelvic veins might* allow a constant stream of eggs to reach the lungs and some might conceivably find their way through the pulmonary circulation and become scattered in the tissues But that hardly explains the finding of nests containing considerable numbers

Fig 348 —Rad ograph of lungs in pulmonary schistosomiasis *early stage* Note the thickened no lular arteries at the bases of the lungs (Photograph s pplie l by M. Erfan Cairo Egypt.)

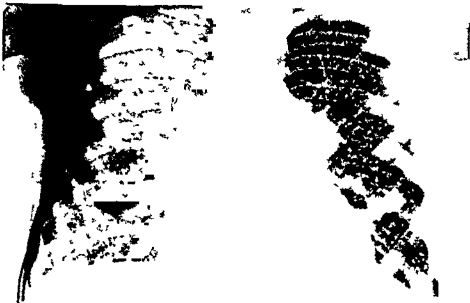


Fig 349 —Radiograph of lungs in pulmonary schistosomiasis *Moderately advanced stage* Note the granular lung fiel ls, nodular arteries increase of the hilar shadows, and prominence of the pulmonary con s. (Photograph supplied by M. Erfan, Cairo, Egypt.)

of eggs in granulomatous lesions of the brain cord or skin as is known to occur Moreover in one case of conjunctival involvement a pair of mature worms was actually found in a branch of the superior ophthalmic vein and presumably they were responsible for the eggs found in the conjunctiva

It is unlikely that worms can mature anywhere else but in the liver so that the ectopic worm must have reached its destination by a route unob

Fig 350 —Radiograph of the lungs in pulmonary schistosomiasis *advanced stage* Note the granular lung fields marked increase of the hilar shadows and marked prominence of the pulmonary conus (Photograph supplied by M Erfan Cairo Egypt.)

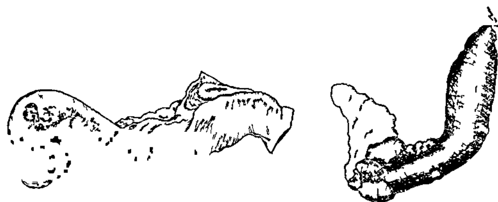


Fig 351 —Two bilharzial appendices removed at operation in an endemic area of *northern Nigeria*. Both show characteristic distortion and surface nodulation with pseudotubercles. (From Lovett Campbell A C 1948 A Note on *Bilharziasis in West African Troops*, Tr Roy Soc. Trop Med & Hyg 41 8 1 8?? by permission of the author)

structed by either hepatic or pulmonary capillaries Faust suggests that such a route exists as is presumed to be the case for malignant metastases in the vertebral system of veins These provide a natural valveless intercommunicating channel to all parts of the body The tissue reaction in ectopic lesions is esentially the same There is an attempt at barrier formation both by proliferation of tissue cells and infiltration of eosinophiles and the formation of epithelioid and giant cells

SYMPTOMS

Symptoms vary with the degree and duration of infection They may be very slight or severe enough to cause death They are conveniently divided into those due to (1) invasion lasting about 3 months (2) oviposition which may go on for 30 years (3) tissue reaction and associated accidents and infections and (4) ectopic lesions

Stage of Invasion

After contact with infested water varying degrees of swimmer s itch develop from a slight tingling to an intolerable itching After a month or 6 weeks general symptoms appear malaise headaches myalgic pains fever with an occasional rigor cough and an urticarial rash on chest and back When localization is vesical loin pain is felt if rectal there may be diarrhea and abdominal pain

Stage of Oviposition

The first symptom is generally a painless hematuria a few drops of blood escaping at the end of micturition Occasionally the whole flow is uniformly blood tinged and clots may be expelled Later some frequency and precipitancy show themselves and a little deep seated perineal pain develops Endemic hematuria may go on for months or years without serious ill health

Prostatic involvement may give rise to hemospermia with rectal localization a slight excess of mucus in formed stools may be all that is noticed or there may be a mucoid diarrhea Later blood and mucus alone may be passed and mild dysenteric symptoms occur but there is little pain or tenesmus

Pain and tenderness over the appendix is not uncommon but acute appendicitis is not a recognized complication

Stage of Tissue Reaction

As reactive fibrosis continues various complications occur Stricture of the urethra leads to dysuria periurethral abscess and fistula The papillomatous excrescences in the bladder are matched by similar overgrowth on the vulva in women Elephantoid deformities of the penis may occur and the spermatic cord may become nodular and the epididymis enlarged Ulceration of the bladder provokes recurrent attacks of cystitis leading to hypertrophy of the bladder wall and diminution of its capacity Vesical stones single or multiple are frequently associated and add to the symptomatology

[illegible] Lesion

[illegible] ...ovascular symptoms are caused
[illegible] Lung lesions are not easily disting
[illegible] The cardiovascular lesions produce
[illegible] ...mbling Ayerza's disease but without c
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...ral nervous system, the presence of bilharzial granulo
[illegible] may cause various local symptoms So far t
[illegible] ...alization have been vague but acute and
[illegible] ...at autopsy to be due to granulomata in th

[illegible] ...containing eggs have been noted both in Eg
[illegible] ...occurring in men who ran a heavy and repeat
[illegible] flank loin and scrotum and appeared about t
[illegible]

...eye, small granulomata containing eggs may be found on t
[illegible] but neither iritis nor keratitis has been reported

General

The chronic nature of this disease associated with blood loss and
...to lower general vitality and predispose to more fatal disease
...is often aggravated by coincident ancylostomiasis and the hem
...in an endemic area may vary from 25 to 50 per cent The supe
...nutritional deficiency tends to produce symptoms of avitaminosis and t
...often supervenes Apparently schistosomiasis can itself produce
...apart from complications

DIAGNOSIS AND LABORATORY FINDINGS

The typical brownish colored terminal spined eggs are diagnostic
they vary from 120 to 150 microns in length and 40 to 60 microns in b
Though degenerate nonviable eggs are seen, more especially during tre
there are no unfertilized eggs Each contains a miracidium which can
actively moving in the egg provided that the osmotic tension
is low Normal urine needs to be dilut... 0 in order the
hatch and the miracidium escape throug... verse ruptur

Urine —It is best to take urine pa... arp exercis
contains no trace of albumin eggs will ... ent This
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eggs Rectal massage of th... of the ... d to th
ing eggs in the urine If ... ne is ... n cas
nephritis the miracidia ma... in th ... void
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previously been found in the urine, they may appear after the slight trauma of cystoscopy, or after rectal massage against a sound or metal catheter passed into the bladder

Rectum—Lesions are found in the rectum in about 3 per cent of cases showing vesical involvement The papillomata in the pelvic colon are flat and not pedunculated as in *S mansoni* infection Eggs are most readily found in any mucus adhering to the fecal mass They can be obtained by use of a rectal swab or by actual biopsy of the mucous membrane Most eggs found in the rectum are nonviable

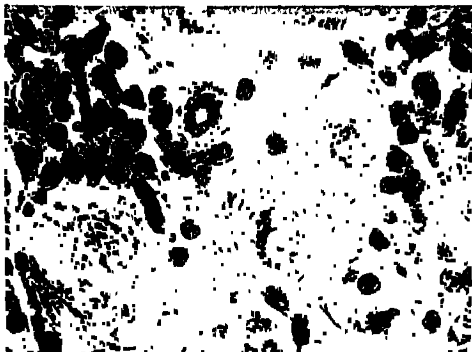


Fig 352—Eggs of *Schistosoma haematobium* in the appendix (case in Northern Rhodesia) These eggs resemble in shape those of *S intercalatum* (Photomicrograph by A C Lovett Campbell.)

Skin Test—Alves and Blair (1946) have made a more specific antigen from cercariae and so improved the original technic of Fairley and Williams (1931) A dose of 0 01 c c injected intradermally causes the initial wheal to increase up to 9 fold in diameter with outrunners and a surrounding erythema in all positive cases This test is useful in mass surveys, it is never negative in those actually passing eggs, and uncovers a higher proportion of cases than repeated urine or fecal examinations

In cases with granulomata in the skin eggs can be found by biopsy

Liver—A small bored double trocar can be used for liver puncture and may reveal eggs, especially in patients with hepatomegaly

Blood —Hemoglobin levels may fall as low as 15 to 20 per cent but mild infections cause little anemia

Eosinophilia may reach as high a figure as 50 to 60 per cent in the invasion period but usually remains between 7 and 15 per cent in chronic infections

Complement Fixation —Fairley first used alcoholic extracts of snail livers infected with *S mansoni* cercariae from which by evaporation he obtained an antigen A saline extract of this can be used as for the quantitative Wassermann reaction It is a group schistosoma reaction and remains positive only as long as living worms persist in the host This is a valuable control of effectiveness of treatment

TREATMENT

The administration of an effective anthelminthic must be the primary aim in treatment but as these may be somewhat drastic very debilitated and anemic patients should be hospitalized and prepared by suitable diet and even blood transfusions if necessary Pyogenic infections of the urogenital organs should be controlled with sulfonamides

Inorganic Antimonials

Tartar Emetic —Potassium antimony tartrate (P A T) This drug was first successfully used in the treatment of kala azar and it was tried out by Christopherson in 1918 He considered that it acts directly on the eggs which soon become degenerate and nonviable Fairley however considered that it acts first on the female reproductive organs and later poisons the worms It is usually given by intravenous injection using a freshly prepared aqueous solution of 0 5 to 1 0 per cent with or without the addition of saline or glucose

When dealing with large clinics a fresh stock solution can be sterilized by boiling for not more than 10 minutes A convenient method for more limited use is to have small tablets of 5 and 10 cg each from which freshly prepared solutions can be made by adding sterile distilled water 1 c c per centigram Dosage will then vary from 5 to 15 c c (5 to 15 cg) for men 3 to 10 c c (3 to 10 cg) for women and 2 to 8 c c (2 to 8 cg) for children

After the first 2 injections of smaller doses at 3 day intervals the full dose can be attained and repeated twice weekly A total of 2 Gm for an adult male of average weight is necessary in order to hope to kill off the worms This requires 12 to 15 injections lasting 4 to 5 weeks It is important that the course should not be interrupted as the worms are apt to recover

A *more intensive treatment* has been advocated by Alves and Blair Using sodium antimony tartrate they claim to be able to reduce the duration of treatment to 24 or 30 hours They used a solution of 1 gr of S A T in 10 c c of 5 per cent glucose (approximately 0 5 per cent) and gave injections every 3 hours Doses of 1 to 2 5 gr are given through a fine needle at a speed not greater than 2 c c per minute The total dose was calculated at 1 gr to 12 pounds' weight

This method though apparently effective in quickly banishing viable eggs and rendering the skin test negative is nevertheless somewhat drastic and in view of the toxicity of the drug must be used with care As standard treatments so frequently fail to cure some more intensive modification is desirable until more specific drugs are available

Toxic Effects of Inorganic Antimony —The most obvious disadvantage of these drugs is the intense reaction they produce in the tissues if there is any escape around the vein which is being injected and phlebalgia quite apart from such accidents General toxic effects are headache nausea vomiting rheumatic pains erythema and desquamation of the skin A violent fit of coughing is often precipitated and old standing lesions of pulmonary tuberculosis may be reactivated Overdose may produce diarrhea and damage to liver and kidneys

During a course of treatment alteration in the electrocardiogram tracings of the heart have been noted indicating a toxic action on the heart muscle Bradycardia may be followed by auricular fibrillation which may end in sudden death

Other Methods of Giving Tartar Emetic —

Rectally Rectal retention enemata have been used and deserve further trial

Orally Keratin coated pastilles have been used and good results claimed by Rincones (1945) in cases of *S mansoni* infection Dosage was about 2 cg per 10 kg given in 2 or 3 doses within 24 hours

The author has found that tartar emetic can be given orally in solution doses of 1 gr three times daily being gradually tolerated without nausea or vomiting

Organic Antimonials

Fuadin (Stibophen Neoantimosan) is a trivalent organic compound—antimony pyrocatechin sodium disulfonate containing 13 6 per cent of antimony It has the advantage that it can be given intramuscularly It is put up in 7 per cent solution in ampules and after preliminary injections of 1 5 c c and 3 5 c c doses of 5 c c are given on alternate days to a total of 45 c c for an adult and proportionate doses for children

Anthiomaline (lithium antimony thiomalate) is another trivalent compound containing 5 per cent of antimony It can be given either intravenously or intramuscularly in doses of 2 c c of a 6 per cent solution on alternate days to a total of 20 c c

Though the toxicity of these organic antimonials appears to be somewhat less than tartar emetic they are correspondingly slightly less effective

Other Drugs

Emetine by intramuscular injection is a general protoplasmic poison which is effective against various trematodes as well as against *Endamoeba*

histolytica It can be given in doses of 0 5 to 1 gr, if antimony is contraindicated *Toxic symptoms, tachycardia,* and muscular weakness may occur at about the tenth dose

Miracil D (Nilodin) is a thioxanthane derivative (1 methyl-4 diethyl amino ethylamino thioxanthane) It is a yellow powder soluble up to 2 per cent in water at room temperature This drug has been recently synthesized and tested in the search for one which will be effective by oral administration Blair et al (1949) have found that in southern Rhodesia it cures 90 per cent of cases of urinary infection with *S haematobium* among native school children The course recommended is a total daily dose, given in 2 portions, morning and evening, of from 15 to 25 mg per kg of body weight

The results are distinctly encouraging and, though some refractory cases occur there is little toxic manifestation

Test of Cure

Absence of eggs, red cells or albumin from the urine for 3 months after treatment is presumptive evidence of cure Confirmation should be sought by noting the absence of any new tubercles on cystoscopy and a negative skin antigen test

SCHISTOSOMIASIS INTERCALATA

DEFINITION

Schistosomiasis intercalata is a chronic disease caused by infestation of the inferior mesenteric veins by adult *Schistosoma intercalatum,* the eggs of which produce mild dysenteric and possibly other symptoms but never invade the genitourinary organs

HISTORY

It is well recognized that in about 3 per cent of cases of infestation with *S haematobium* eggs are found in the feces as well as in the urine Clapier (1920) observed 5 patients in the Congo in whom terminal spined eggs were found exclusively in the feces and not in the urine

Chesterman (1923) reported 13 similar cases from Yakusu near Stanleyville Belgian Congo and called attention to the different shape of the eggs which were larger, more spindle shaped, and carried a more pronounced terminal spine than typical eggs of *S haematobium* He recovered 3 adult males and 1 female from a limited autopsy The wall of the pelvic colon was packed with eggs but none were found in the vesical mucosa *Bifid tailed cercariae were found in local snails which were identified as Bulinus africana*

Fisher (1934), working at Yakusu made a full study of this schistosome and, on the basis of its invariable and exclusive intestinal localization and the size and shape of its eggs found in the feces of human patients and laboratory infected mice, suggested that this was a new species which he named *Schistosoma intercalatum*

CAUSAL AGENT

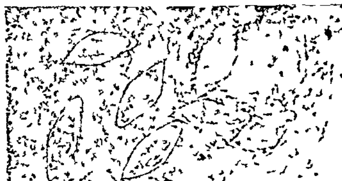
Schistosoma Intercalatum Fisher, 1934 (?)

The adult worms, as bred in white mice are indistinguishable *morphologically* from *S haematobium* on the one hand and *S bovis* on the other

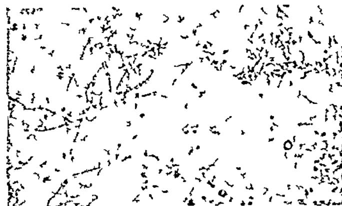
The *male* measures 11 to 14 mm. in length by 0 3 to 0 4 mm in width when not unfolded The testes vary from 3 to 5 in number, usually 4 The *mature female* is 10 to 14 mm long with a maximum diameter of 0 15 to 0 18 mm The eggs are intermediate in shape and size between those of *S haematobium* and *S bovis*



F g 353



F g 354



F g 355

F g 353 —Male and fema e of *Schis osoma in erca atum* In copu a. F xed by lacto-p en (×14 1934

Fisher

perime Trop. au 10

The Vector

Fisher, though unsuccessful in attempts to infect the local snails with miracidia, readily obtained fork tailed cercariae from 2 to 3 per cent of the prevalent I. africana which infested the small creeks along the Congo river. These readily grew to adults in white mice.

PATHOLOGY

Sigmoidoscopy reveals characteristic lesions between the anal canal and *the pelvirectal junction*. The *affected* mucosa has a granular appearance resembling coarse sandpaper appearance being studded with petechial papules varying in size from a pinhead to 4 cm. Neither ulceration nor polypi was observed. Cystoscopy has never revealed any bladder pathology.

CLINICAL SYMPTOMS

In the endemic area a fecal census revealed a 96 per cent infestation rate in the lower age group but eggs were rarely found in the group over 30 years. The centrifuged urine of 100 infected persons was uniformly negative for eggs. The *invasion period* in native children is not marked by any urticarial symptoms. The *splenic index* is no higher than in controls but hepatomegaly is frequently noticed.

Stage of Oviposition

Symptoms are generally much less severe than in other forms of bilharziasis. Abdominal pain and mucosanguineous dysentery without toxemia are the usual complaints. From the localization of the parasites in the mesenteric veins one would not expect pulmonary manifestations as readily as in *S. haematobium* infestation and it has not been proved that they actually occur. There is no reason why they should not, as *S. mansoni*, also an inhabitant of the mesenteric veins, is not uncommonly found in the lungs as also are its eggs. Eggs have never been found in the sputum though this is occasionally blood stained in cases of pneumonitis occuring in young folk with rectal infection. The author has seen one case which clinically appeared to suggest a cerebral localization.

Cases of hepatosplenomegaly also occur suggesting a resemblance to *the* visceral schistosomiasis of *S. mansoni* infestation.

In the few cases diagnosed among Europeans the only symptoms were abdominal discomfort and the passage of blood and mucus.

IMMUNOLOGY

A certain degree of acquired immunity to reinfestation is suggested by the failure to infect adult volunteers in an endemic area. They rarely manifest any symptoms.

LABORATORY FINDINGS

The characteristic eggs are readily seen in intestinal mucus whether clean or scraped from the surface of the fecal mass. A rectal swab, a gentle curettage through a proctoscope will often reveal eggs.

TREATMENT

Inorganic antimony gives similar results to those obtained in *S haematobium* infestation There is no record of a trial of organic antimonials or of Miracil D in this disease

Acriflavine, 2 per cent aqueous solution given orally has proved moderately effective in this type of schistosomiasis Doses of 2 to 10 c c according to age were given on an empty stomach on 3 successive days Eggs disappeared from the feces in 3 to 6 days Degenerate eggs are rarely seen It is not known whether this treatment kills the schistosomes but it is sufficient to alleviate symptoms can be easily given and repeated if necessary and is not attended with the disadvantages of antimonial treatment

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CHAPTER 47

SCHISTOSOMIASIS MANSONI

J ALLEN SCOTT

The blood fluke, *Schistosoma mansoni*, causes a disease correctly known as schistosomiasis mansoni, but frequently called intestinal bilharziasis or intestinal bilharziosis

It occurs in many parts of Africa and in certain tropical regions of the Western Hemisphere, notably in Brazil, Dutch Guiana, Venezuela, and some of the Antilles east of Haiti Since it is transmitted by only a few species of snail vectors, the geographic distribution of the disease is limited by the distribution of these vectors and, with a few exceptions to be mentioned later, the disease now occurs wherever appropriate snails are present

The manifestations of the disease are related principally to the passage of the parasite eggs through the intestinal mucosa, and their accumulation in the liver, to which they are carried by the portal circulation In respect to pathogenesis schistosomiasis mansoni resembles schistosomiasis japonica more closely *than it does schistosomiasis haematobia, while its geographic distribution* overlaps that of the latter

CAUSAL AGENT

Schistosoma Mansoni Sambon 1907

Synonyms—*Distoma haematobium* Bilharz, 1852, *pro parte*, Bilharz, Looss, et al., *Schistosomum americanum* da Silva 1909

The *adult worms* of *S mansoni* differ from those of the other species of the genus by minute but distinctive characters which have little importance from the clinical point of view, since specific diagnosis is almost invariably determined by the type of eggs found in the discharges or in pathologic material The *female worms* are very slender and thread like, averaging approximately 0 33 mm in diameter and about 1 to 1 5 cm. in length The *males* are somewhat shorter and thicker, averaging slightly less than 1 cm. in length and about 0 5 mm in diameter when measured with the folds of the gynecophoric canal rolled inward to form a tube The adult worms inhabit principally the venules of those branches of the portal vein which drain the colon and rectum It has been commonly supposed that the female worm remains almost constantly held in the gynecophoric canal of the male, but Faust, Jones, and Hoffman (1934) state that permanent pairing appears to be the exception rather than the rule, at least in their experimental animals The eggs are laid singly or a few at a time in the terminal and subterminal venules of the submucosa

The fate of these eggs after they are deposited in the venules is quite diverse, but for purposes of discussion they can be considered in three groups In the first place, some of the eggs are carried with the blood stream to the liver or occasionally to other organs This group of eggs serves no biologic purpose as they eventually become destroyed in the tissues, but pathologically they are of great significance In the second place, some eggs *are extruded* through the walls of the venules into the mucosa and eventually reach the

lumen of the intestine The eggs of the third group are s milarly extruded into the mu cosa submucosa or other tissues and are there immol l zed and eventually destroyed The mechanism by which the eggs are extruded from the venules is discussed below in con nection with the pathologic damage they cause in the process

The experiments of Faust Jones and Hoffman lead to the conclusion that each ma ture female probably lays from one hundred to se eral hun lred eggs per day l ut only a small fraction succeed in leaving the body of the host Because of the number of worms in each person and the high proportion of nfected persons in endemic areas the total number vo ded in a locality may be enormous In many parts of Venezuela for example a few people were passing as many as 750 000 eggs per la 10 per cent were pass ng more than 100 000 40 per cent more than 20 000 an l 0 per cent were passing varying numbers up to 20 000 (Scott 1940a)

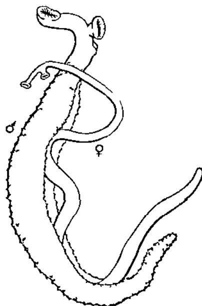


Fig 356—Drawing of adult *Sch stoso na mansoni* worms sl owing slen ler fen ale l el l in the gynecophoric canal of the male

A small proportion of the worms local ze in the blood vessels of the urinary bladder and some eggs are tl us p i se l with tl e ur ne For tl e most part ho vever the eggs wh ch carry on the l fe history of th s species are those passed with the feces In Egypt it was foun l (Scott 1937b) that 15 per cent of the positive cases were passing eggs in the ur ne and one third of th s group passed eggs only in the urine as far as could be determ ned from ro itine exam nat ons

In appearance the *eggs* of *S mansoni* can be l fferent ated from those of other species by the very prominent lateral sp ne Faust and Hoffman (1934) measured 500 live eggs from a case in a human l e ng and foun l them to average 142 microns in length but there is a considerable variab l ty above and belo v this size as shown by their coefficient of variat on of " per cent As a r le the eggs contain living larvae l ut even when they have collapsed and the sl ell is rolled into a wrinkle l mass they can usually be recognized and positively identife l in microscop c p reparations made for l agnostic purposes. A few eggs are passed after tl ey have l een held in the t ss ies for such a long time that the larvae in them are dead In cases wh ch have received treatment, the eggs frequently

do not contain live larvae, but have a darkened appearance The significance of these eggs as a measure of the success of treatment is mentioned below

Hatching of the eggs is brought about when they fall into fresh water The mechanism involved in this process has been extensively studied, and although other *factors may* be involved, the change of osmotic pressure is probably the principal one In the laboratory, diluting the feces with distilled water, allowing them to settle, pouring off the water, and repeating several times will usually cause them to hatch

The larva which hatches from the egg is similar to those of other trematodes and is called a *miracidium*

The life of the miracidium is seldom over 24 hours and miracidia may survive only a few hours unless they are released in the vicinity of snails which can act as intermediate hosts They are attracted to the snails and swim to a position in contact with the tentacles or the "foot" of the snail Holding themselves in contact by the action of their cilia they secrete a histolytic substance from their glands, which dissolves a portion of the external tissues of the snail to make a point of penetration



Fig 357 —Photomicrograph of an egg of *Schistosoma mansoni* containing miracidium and an empty egg shell (Courtesy of Horace K. Giffen)

Once the anterior end of the miracidium has been inserted into tissues it continues to enter slowly by the expansion and contraction of its flexible body Once inside the tissues the larvae begin to migrate toward the digestive gland of the snail which is located in the inner whorls There it develops into a more or less sac like organism known as a *primary sporocyst* In each primary sporocyst several *secondary sporocysts* develop These break out of the primary sporocyst, and in them in turn a second type of larva known as a *cercaria* develops At any one time the secondary sporocyst may contain a number of cercariae in various stages of development As they become mature they break out of the sporocyst into the lymph spaces of the snail and eventually emerge into the water

This development from miracidium to cercaria requires approximately 3 weeks and can be loosely called asexual reproduction since no merging of two sexual elements occurs It seems evident that the sex of the miracidium is predetermined, since a snail infected with a single miracidium will produce cercariae of only one sex The production of cercariae continues over a long period of time In the case of snails infected with

s ngle m rac d a several thousand cercar ae ha e been produced ea h da for per ods of several months total ng 100 000 cercar ae n son e ca s

In nature the cercar ae usually en e ge f o the a l n gro ps espec ally in the morn ng Lal oratory stud es nd cate tlat the t m l s wl cl pro luces th s da ly emergence s prol ably a co b nat on of tl e a wa er a l tle exjo ure to l ght sunl ght The pr nc j al lara ter t wl h i t gu l s l sto one cercar ae from those of other tre atoles s the presence f a f kel ta l The pr nc pal character st cs by wh ch the cercar ae of *S mon n* a l j el l ff rent atel from tle other two human spec es are tle number an l chara ter of t t t j of glan l cells Tl ese cells are very d fficult to count ho e er an l n j t al k ther are other le er t al d f ferent at ng character st cs wh cl can le us l

The cercar ae are most act e dur ng tle n ldle of he day in shallo s pools read ly warmed l tle sun Tle rarel l e he ate o e han l ours an l any have lost the r v gor l tle end of 4 ho s l x j ne a l tle ha e l een sl own to jass sand filters but n pract ce f ltrat on and hlo a e ler publ c water suppl es virtually safe Sn all quant t es of water an o t a l re lere l safe by heat ng and large quant t es of unfiltere l water for ba h g purj a le n a le safe l the alternate use of ² storage tanks of suel s e that tle a l l l a l a t 48 hours l efore us

C rcar ae are app rently attra t l o l k n of hu an l e ng l o e form of cl em ical attract on an l ujon reach ng t tle a ta l l el e t the sk l eans of the suckers The tubules of the gla l cell e l n h ll w j ted sj ne wh ch a e apparently u el to p erce tle sk n l le tle er ar l ol l lf ghtl atta l el ly means of tle oral sucker The g a d cell tl en e ete a l t l l tance h ch helps nake an open ng in tle sk n for tle penetrat on of the cercar a Tle backward po nt ng sp nes over the bo l of the cercar a a l n j re t g an e o as soon as the anter or end has ol ta ne l entrance nto the sk n The o ga so fl x l le tl at t can enter througl a very small hole Tle ta l does n t n the k th tle cercar a b t s sloughe l off outs le It has l een sl own b Bra kett 1939 that f a person real zes l e has exposed h mself to water conta n ng tle er ar ae mme l at act on an be taken to prevent pene trat on Var ous solut ons l a e be u e l for th s purj o e but Bra kett foun l that the most effect ve means was go s r l l g l a ars t wel Tle react on of the skin to the penetrat on of the cer a ae l l l l n re at o to tle pathology

As soon as the ce c r a h l t ts n l a l j ene rate l nto the skin t can be call d a *metacer a a* an l furtl r l l pn n of le l rg a j r un ally l eg ns at on Faust Jo es an l Hoffman 1934 l a ho l rat autops ed 16 hours after in fect on the lar ae co ld l e reco er l n l f n the l p r la ers of the skin In those autops ed ² ho rs after nfe t on ll t ll l found n the cor u l ut n o t of them ha l passe l nto tle l l od s el a l w e le g a re l w th the blood stream to tle lungs Var ous l n j l o les sl o l le n l at ng that the l ar ae ha l jasse l through the In an als aut j e l at 4 l u la ae were foun l n the skin but it s not prol al le that all of the la ae ha l es aj e l f tle j e pl eral t es l v th s t me s nce at e en later p r o ls lar ae were fo l n the r g lt heart a l the nfer or vena cava. The larvae continued to acc n late n the aj l aries of the lungs up to 0 hours or mo e Tle we e foun l for the fi t t e n the left l ea t f an an nal k lle l 86 hours after infect on in l at ng that l tlat t me they ha l been al l to pass through the cap llar es of the lungs

As the lar ae are l str l ute l tl ro gho t the bo l w tl tle l l od from tle left heart many are le tro e l the aj llar es l t s me app ar t e re late aga n tl rough the heart an l lungs Th re h g tle l ver beg n to fe l an l t has been supj osel that they re t a n there l ut Fa t l e an l H ffma (1 34 ha e foun l lar ae wh ch show s gns of ha ng fe l in the l er e re lat ng aga n th o gh the l ngs A certa n amount of level p ent occurs as so n as the lar ae nte tl l o l l ut the act e j las s of growth an l le elop ent do n t reall beg n unt l the lar ae l a e reacl ed the l ver Some larvae appeare l n tle l e as ea l as tle se enth la O the n netee th lay they seeme l to be acc n u at ng the e n la ge n nbers for tl fir t t n e an l n the twent th rd lay

most of them were in the liver At this time a few worms, about 1 5 mm. in length, were found in the mesenteric veins From the thirtieth to the fortieth days many worms were found in the mesenteric veins, but not until the forty seventh day were any of them foun to be mature Since the animals used for these experiments are not natural hosts of thi species, it is not certain how nearly the conditions duplicate those present in human be ings It is interesting to note in passing that at a time when most of the worms were found in the mesenteric veins a few immature forms were frequently found in the lungs They were usually in the alveoli and were invariably surrounded by neutrophiles, eosino philes, and macrophages The authors mentioned above report that an assistant, who ac cidentally infected himself in the laboratory, passed eggs for the first time on the forty second day, and that the similar prepatent period for worms in experimental animals wa slightly longer

THE VECTORS

Many species of snails have been listed as vectors of *S mansoni* Lane (1936) has pro vided a summary of the literature in this field Since it is difficult to differentiate between the cercariae of the different species of human and animal schistosomes, it is possible that in fection with *S mansoni* has been erroneously reported for many species of snails A further complication is the fact that the taxonomy of the snails of this group is still very much in flux and various authorities in the field do not agree on which names should be used It seem probable that all of the vectors of *S mansoni* belong to what was originally the genu Planorbis The principal vector in Egypt and some other parts of Africa is *P boissyi* In other parts of Africa *P pfeifferi* is the principal snail involved When *S mansoni* was first found in snails in the Western Hemisphere, Lutz (1916) incriminated *P olivaceus* in Brazil and later (1917) reported the infection from several other species of the same genus Iturbe and Gonzalez (1917) meanwhile had reported the vector in Venezuela to be *P guadeloupensis* Since then these names have been changed The genus has been divided and no American snails bear the name Planorbis

Pilsbry (1934) described the genus Australorbis which includes all verified natural vec tors He also showed that *P glabratus* Say, 1818, is the same as *P guadeloupensis* Sowerby, 1821, hence the former name is now used along with the new generic name Australorbis Since then several studies (Martins, 1938, Scott, 1940b) have shown that all of the vectors re ported for the Western Hemisphere intergrade and, therefore, should be considered as the same species, ***Australorbis glabratus*** Jansen (1944) does not accept this latter conclusion, but it seems likely that the differences involved may prove to be no more than geographic, ecologic or physiologic races

Wherever a large percentage of the population is infected, the snails are usually found with ease, and elsewhere the case reports must be substantiated by collections of snails made by recognized authorities, or by specimens deposited where they will be available for study

In Brazil, the snails and the infection occur along the east coast and back into the interior for only a few hundred miles, from a point somewhat north of Rio northward to the state of Ceará They are not present in the Amazon valley nor in the interior to the south, although imported cases have been erroneously reported as indigenous to these re gions The snails and the schistosomes are present in Dutch Guiana, but not in British or French Guiana In Venezuela the infection is limited by the distribution of the snail to the north central part of the country (Scott, 1942), although a small focus probably did exist at one time in Cumaná in eastern Venezuela Reports of cases of the disease west of the basin of Lake Valencia in north central Venezuela are all based on infections con tracted elsewhere, as are those reported in the countries of South America further west Among the cases reported from Central and North America, none has proved to be in digenous In the West Indies the distribution is again spotted No infection has been reported from Trinidad, and the snails are apparently uncommon there although Faust (1935) stated that they had been found With the exception of St Lucia, where a small focus may possibly exist, the snail vectors do not occur east of Martinique where they are abundant On Guadeloupe proper, Bartsch (1946) did not find them, but they are

abundant on the island called Grand Terre They are present on Antigua and St. Kitts. This latter island is interesting in that wild monkeys of African origin are infected The human beings are also infected here so it is not known whether these animals really play a part in the epidemiology of the infection This is the only case on record of animals being infected with this species under natural conditions in the Western Hemisphere The infection is present in Puerto Rico and Vieques Island but is not indigenous in the Virgin Islands or the Bahamas In the Dominican Republic the disease has been reported, but if it is indigenous, its distribution is limited The snails have not been found in extensive surveys of Haiti Cuba or Jamaica

The possibility of introduction of the disease into new areas is an important question and one which has received considerable study in the United States during the war because of the return of servicemen infected in various parts of the world These studies have centered on the possibility that the infection might become adapted to some species of snails now present in the United States The other possibility that the known vectors can spread into new areas is also of importance and is discussed below Of the very large series of species tested as possible hosts of *S mansoni* only one species has proved to be at all susceptible (Cram Jones and Wright, 1945) Of 12 specimens of *Tropicorbis havanensis* tested, these authors were able to infect 3 Cram and Files (1945), in a later report on the same studies, state that a relatively small percentage of this species of snails proved susceptible to infection In one case cercarial production was continued for as long as 107 days, the output increasing throughout this period and resulting in death of the snail Stunkard (1946) tested hundreds of snails of this species using specimens which were bred from the stock used by the above authors and apparently the same West Indian strain of *S mansoni*, but cercariae were never obtained The available information does not indicate that this snail has an extensive distribution in the United States It is interesting moreover, that Stunkard found that this West Indian strain of *S mansoni* would not develop to the cercaria stage in Egyptian specimens of *P boissyi*, the usual vector in Egypt His final conclusion is that there is little likelihood that the human schistosomes will be established in the U S, but he makes what seems to be a valid point that this adaptability of trematodes is a matter which should be taken into consideration On the other hand there are also other limiting factors mentioned below in connection with a discussion of the epidemiologic cycle

The possibility that the present vectors may extend their range is a matter deserving consideration Little is known of the factors which now limit their distribution, but certain facts are of interest Wherever any species of schistosome is really common and widespread irrigation is practiced In Egypt *S haematobium* infects a high percentage of the population only in regions of perennial irrigation (Scott 1937c) Most of the enormous number of cases in China occur in irrigated regions of the Yangtze Valley (Faust and Meleney, 1924) Recent reports from Japan and the Philippine Islands reveal the importance of irrigation there In Venezuela it is doubtful if the snails could maintain themselves long in the absence of irrigation, except in Lake Valencia where they do not transmit the infection (Scott 1942) In Puerto Rico the infection is exclusively associated with irrigation projects (Hoffman and Faust, 1934), while in Brazil the most serious infection is again in irrigated regions of the northeast In other parts of Brazil as in the unirrigated parts of other countries, the infection is either light localized, or reported from areas where inadequate information is available

Even where irrigation is not a limiting factor, sharp limits to the distribution of the vectors have often been observed but not adequately explained In Egypt, for example *Planorbis boissyi* is present in the delta of the Nile, but

most of them were in the liver At this time a few worms, about 1.5 mm. in length, were found in the mesenteric veins From the thirtieth to the fortieth days many worms were found in the mesenteric veins, but not until the forty seventh day were any of them found to be mature Since the animals used for these experiments are not natural hosts of this species, it is not certain how nearly the conditions duplicate those present in human beings It is interesting to note in passing that at a time when most of the worms were found in the mesenteric veins a few immature forms were frequently found in the lungs They were usually in the alveoli and were invariably surrounded by neutrophiles eosinophiles, and macrophages The authors mentioned above report that an assistant, who accidentally infected himself in the laboratory, passed eggs for the first time on the forty second day, and that the similar prepatent period for worms in experimental animals was slightly longer

THE VECTORS

Many species of snails have been listed as vectors of *S mansoni* Lane (1936) has provided a summary of the literature in this field Since it is difficult to differentiate between the cercariae of the different species of human and animal schistosomes, it is possible that infection with *S mansoni* has been erroneously reported for many species of snails A further complication is the fact that the taxonomy of the snails of this group is still very much in flux and various authorities in the field do not agree on which names should be used It seems probable that all of the vectors of *S mansoni* belong to what was originally the genus Planorbis The principal vector in Egypt and some other parts of Africa is *P boissyi* In other parts of Africa *P pfeifferi* is the principal snail involved When *S mansoni* was first found in snails in the Western Hemisphere, Lutz (1916) incriminated *P olivaceus* in Brazil and later (1917) reported the infection from several other species of the same genus Iturbe and Gonzalez (1917) meanwhile had reported the vector in Venezuela to be *P guadeloupensis* Since then these names have been changed The genus has been divided and no American snails bear the name Planorbis

Pilsbry (1934) described the genus Australorbis which includes all verified natural vectors He also showed that *P glabratus* Say, 1818, is the same as *P guadeloupensis* Sowerby 1821, hence the former name is now used along with the new generic name Australorbis Since then several studies (Martins, 1938, Scott, 1940b) have shown that all of the vectors reported for the Western Hemisphere intergrade and, therefore, should be considered as the same species, *Australorbis glabratus* Jansen (1944) does not accept this latter conclusion, but it seems likely that the differences involved may prove to be no more than geographic, ecologic, or physiologic races

Wherever a large percentage of the population is infected, the snails are usually found with ease, and elsewhere the case reports must be substantiated by collections of snails made by recognized authorities, or by specimens deposited where they will be available for study

In Brazil the snails and the infection occur along the east coast and back into the interior for only a few hundred miles, from a point somewhat north of Rio northward to the state of Ceara They are not present in the Amazon valley nor in the interior to the south, although imported cases have been erroneously reported as indigenous to these regions The snails and the schistosomes are present in Dutch Guiana, but not in British or French Guiana In Venezuela the infection is limited by the distribution of the snail to the north central part of the country (Scott, 1942), although a small focus probably did exist at one time in Cumaná in eastern Venezuela Reports of cases of the disease west of the basin of Lake Valencia in north central Venezuela are all based on infections contracted elsewhere, as are those reported in the countries of South America further west Among the cases reported from Central and North America none has proved to be indigenous In the West Indies the distribution is again spotted No infection has been reported from Trinidad and the snails are apparently uncommon there although Faust (1935) stated that they had been found With the exception of St Lucia, where a small focus may possibly exist, the snail vectors do not occur east of Martinique where they are abundant On Guadeloupe proper, Bartsch (1946) did not find them, but they are

abundant on the island called Grand Terre They are present on Antigua and St Kitts. This latter island is interesting in that wild monkeys of African origin are infected The human beings are also infected here so it is not known whether these animals really play a part in the epidemiology of the infection This is the only case on record of animals being infected with this species under natural conditions in the Western Hemisphere The infection is present in Puerto Rico and Vieques Island but is not indigenous in the Virgin Islands or the Bahamas In the Dominican Republic the disease has been reported, but if it is indigenous its distribution is limited The snails have not been found in extensive surveys of Haiti, Cuba, or Jamaica

The possibility of introduction of the disease into new areas is an important question, and one which has received considerable study in the United States during the war because of the return of servicemen infected in various parts of the world These studies have centered on the possibility that the infection might become adapted to some species of snails now present in the United States The other possibility that the known vectors can spread into new areas is also of importance and is discussed below Of the very large series of species tested as possible hosts of *S mansoni* only one species has proved to be at all susceptible (Cram, Jones and Wright, 1945) Of 12 specimens of *Tropicorbis havanensis* tested, these authors were able to infect 3 Cram and Files (1945), in a later report on the same studies, state that a relatively small percentage of this species of snails proved susceptible to infection In one case cercarial production was continued for as long as 107 days, the output increasing throughout this period and resulting in death of the snail Stunkard (1946) tested hundreds of snails of this species using specimens which were bred from the stock used by the above authors and apparently the same West Indian strain of *S mansoni*, but cercariae were never obtained The available information does not indicate that this snail has an extensive distribution in the United States It is interesting moreover, that Stunkard found that this West Indian strain of *S mansoni* would not develop to the cercaria stage in Egyptian specimens of *P boissyi* the usual vector in Egypt. His final conclusion is that there is little likelihood that the human schistosomes will be established in the U S, but he makes what seems to be a valid point that this adaptability of trematodes is a matter which should be taken into consideration On the other hand there are also other limiting factors mentioned below in connection with a discussion of the epidemiologic cycle

The possibility that the present vectors may extend their range is a matter deserving consideration Little is known of the factors which now limit their distribution, but certain facts are of interest Wherever any species of schistosome is really common and widespread irrigation is practiced In Egypt *S haematobium* infects a high percentage of the population only in regions of perennial irrigation (Scott, 1937c) Most of the enormous number of cases in China occur in irrigated regions of the Yangtze Valley (Faust and Meleney, 1924) Recent reports from Japan and the Philippine Islands reveal the importance of irrigation there In Venezuela it is doubtful if the snails could maintain themselves long in the absence of irrigation, except in Lake Valencia where they do not transmit the infection (Scott, 1942) In Puerto Rico the infection is exclusively associated with irrigation projects (Hoffman and Faust, 1934), while in Brazil the most serious infection is again in irrigated regions of the northeast In other parts of Brazil, as in the unirrigated parts of other countries, the infection is either light, localized, or reported from areas where inadequate information is available

Even where irrigation is not a limiting factor, sharp limits to the distribution of the vectors have often been observed, but not adequately explained In Egypt, for example, *Planorbis boissyi* is present in the delta of the Nile, but

not in the valley just above In Venezuela, the western and southern limits of the distribution of Australorbis are rather sharp, but beyond them Tropicorbis is abundant in environments which differ in none of the many physical and chemical factors which have been studied (Scott, 1940a) These and other similar observations give us a strong hope but no proof that the present vectors will not spread to new areas Certainly the introduction or extension of irrigation projects in regions where the infection now exists is the factor which should be of greatest concern to public health authorities

Reduction of the snail population seems to be the most hopeful means of controlling schistosomiasis, but this method can usually be successful only when used in conjunction with other possible methods The applicability of these various methods is related to the factors in the epidemiologic cycle Each of these factors is essential to the continuance of the cycle and, could one be eliminated, the disease would thereby be brought under control

Except for the minor case already mentioned, animals are not infected in nature and infection of human beings is, therefore, the first essential factor in the epidemiology of schistosomiasis To control the disease by reducing the amount of infection in the human population has been the object of the mass treatment program which the Egyptian government has carried out through the last quarter century Although this program has been valuable in preventing many cases from reaching the serious advanced stages, it has failed to control the disease, as is evidenced by the lack of any effect on the prevalence of infection (Scott and Barlow 1938)

The second factor in the cycle is the pollution of water Sanitation may be the ultimate means by which this disease is brought under control The difficulties of introducing sanitation into many parts of the world and the still greater difficulties of insuring that a large proportion of the people use these facilities are so great however, that ultimate control by this means is obviously a matter for the far distant future

The third factor has already been mentioned namely, the fact that transmitting snails must be present in the water which becomes polluted It is this factor which seems most susceptible to modification for the purpose of controlling the disease Eliminating the snails from an area will interrupt the cycle of the disease What is more important, it seems highly probable that if the number of snails is maintained at a low level the chances of infection will be so low that the cycle will slow down and finally reach a point where transmission is not adequate to maintain the species For this reason many studies have been made on the biology of these snails, and control measures based upon these studies have been proposed (Barlow, 1937, Scott, 1940a, Luttermoser and Castellaños, 1945) Chemical means for eliminating the snails are of value in limited areas Humphreys (1932) reports that in the Gezira area of the Sudan a commercial carbolic acid was introduced into the irrigation canals and served as a very important part in the reduction of snails in that area Archibald (1933a) has pointed out that the fruit of the tree *Balanites aegyptiaca* is toxic to snails and the possible uses of this fruit have been widely discussed No

large scale experiments have been undertaken and it is not likely to become an important factor in control. Pinto (1944) has undertaken experiments to demonstrate that other plants can be used as a means of control. For snails living in acid waters, such as the vectors of *S. japonicum*, the use of lime is undoubtedly of value. Luttermoser (1941) has had some success in using lime for killing Australorbis in Venezuela, even though they live in alkaline water with a considerable lime content. In the laboratory, copper sulfate can be used in a dilution which will kill snails without harming valuable fish. In nature, however, the presence of varying amounts of organic matter in the water limits the use of this chemical to small bodies of water where the proper dose can be determined by a preliminary test. Where no valuable fish, domestic animals, or human beings will be affected, an excess can be introduced. Copper carbonate introduced for the control of schistosome dermatitis in the U. S. (Brackett, 1940) is somewhat more useful in that it is so slightly soluble in water that an excess can be used without producing too great a concentration in solution. The chief difficulty in the way of using chemical means of control is, however, that the quantity of water in irrigation systems is so great that adequate distribution to all parts of the system is virtually an impossibility. As an adjunct to other means of control it can be very important.

Since the vectors of *S. mansoni* are all strictly aquatic rather than amphibious, as are those of *S. japonicum*, periodic drying of irrigation canals has long been considered a possible means of control. In Egypt Leiper (1915) suggested this means, but Barlow (1933) showed that snails drying in the canal bottom as the moisture slowly disappears protect themselves with a plug of mucus and do not die as quickly as they do when dried on a laboratory table. Many snails will live in the canals without water throughout the usual 40-day period of "winter rotation." Moreover, snails appearing dry and dead at the end of this 40-day period were transferred on the dried mud to a dry, shaded place exposed to the normally high Egyptian temperature. At the end of 4, 5 and 6 months, respectively, some of these snails were put in water and in each case a few revived and later laid eggs (Barlow, 1933). Archibald (1933a) has confirmed these observations for the Sudan and noticed that there the snails are especially apt to pass through dry periods in the deep cracks which appear in dried mud. The author has observed that *A. glabratus* is also similarly protected from drying in Venezuela.

A system of control called "canal clearance" has been worked out by Barlow (1937) in Egypt. On a regular schedule the aquatic plants and the top layer of mud from the canal bottom is thrown out on the bank. The quick exposure to the sun kills most of the snails and the absence of plant growth in the canals prevents rapid breeding of those that find their way back into the canal. As a means of control this system is economically feasible since irrigation practice is thereby improved. In Venezuela this system is not practical, however, partly because of the topography and partly because large aquatic plants are not usually present in the canal and the snails commonly feed on a thin film of algae lining the sides of the canals (Scott, 1940a).

The most important part of a control program proposed for Venezuela (Scott 1940a) is the elimination or reduction of snails by building them out of the irrigation system Methods of canal construction used for purposes of malaria control need to be only slightly modified to fit the biologic conditions under which these snails breed The changes should eliminate residual pools which remain when irrigation water is not flowing and provide for complete draining of all canals whenever they are not in actual use Provision for more prompt and complete draining of the surplus water from the fields would also be necessary All of the available evidence indicates that if the snails were removed by manual or chemical methods from the places where they are most abundant they would not be able to re establish themselves in an irrigation system which is properly constructed and maintained Reduction in cost of maintenance and the increase yield to be expected should pay for the reconstruction and the necessary supervision as has been adequately demonstrated in connection with malaria control projects Luttermoser and Castellaños (1945) have extended these observations and confirmed the conclusions by additional experimentation

The next factor in the epidemiologic cycle of schistosomiasis can be called favorable conditions" These conditions are much too extensive to discuss here but they include both known and unknown environmental factors which must be added to the factors already discussed before there can be development of cercariae

Finally to complete the cycle to the point of additional human infection there must be human contact with the water containing cercariae Under tropical conditions it is inconceivable to think that laborers will irrigate fields without making such contacts Their contacts at the most critical places could be reduced however and the provision of a safe supply of domestic water would eliminate the contacts made by women and children when engaged in household tasks

There are many points in this epidemiologic cycle at which control may be applied The best point for each area and the method of applying the control at each point will need to be determined by the local conditions It would now seem that ultimate control in any area should be merely a matter of sufficient study to develop a program adapted to the local conditions and sufficient money to apply it In many places the resulting economic improvement will be sufficient to ultimately cover the cost

PATHOLOGY

The pathology of schistosomiasis mansoni has received a great deal of study for more than half a century and the literature is so vast that only a few representative papers can be mentioned here Clinical discussions usually follow the classification of Girges (1932) who divided his cases into two types the intestinal and the hepatic or visceral Koppisch (1941) believes that from the pathologic point of view these two types are merely two stages in the

full development of the disease This classification has arisen because most cases seen by clinicians are already well advanced and fall into two more or less distinct groups

In those whose symptoms are primarily associated with an intestinal pathology it seems reasonably clear that damage to the liver has not had time to develop In the other group the obvious manifestations of a pathologic derangement of the liver outweigh the significance of any intestinal symptoms that may still be present

There is undoubtedly much variability between patients as to the severity of the intestinal symptoms and as to the length of time before they are superseded or overshadowed by the more slowly developing liver damage This variation *is probably related to the immune state of the individual* *It should* not be forgotten that this parasite in common with most other helminths does not multiply in the body and therefore the number of worms acquired and the rate of acquisition is of great importance in determining the type of pathologic damage A person receiving a large dose of worms on his first exposure reacts differently from one who has spent his entire life in an endemic area and has acquired his worms a few at a time since early childhood (Hutchison 1928) Direct evidence of immunity in this disease is lacking but many aspects indicate that the situation may be fundamentally similar to that demonstrated in hookworm disease The slow acquisition of hookworms over a long period of time stimulates an immunity which not only prevents the acquisition of further infection but may cause many of the worms already established to be expelled The similarity between the two diseases could be masked by factors related to the different habitats of the two species The hookworms being located in the intestine may frequently be dislodged by influences which are not severe enough to kill them More important however is the fact that even in hookworm disease the immunity is not absolute but a few worms are usually left after the majority have been lost With no quantitative methods applicable to schistosomiasis the continued passage of eggs by a few remaining worms might hide a great reduction in their numbers Furthermore, the schistosomes have a much greater span of life and their most serious effects build up more slowly Once the damage reaches a certain point it continues to progress even in the absence of further stimulation and is not as easily reparable after the worms have been killed

The fundamental pathologic effects of this disease can be roughly divided into four types First the cercariae in penetrating the skin cause some temporary damage Second the adult worms occasionally cause serious reactions especially when in unusual locations Third many effects have been attributed to toxins or metabolic products of the worms even though no specific toxin has been demonstrated Finally the most serious and extensive damage is due to the deposit of eggs in the tissues

The reactions caused by the penetration of the cercariae through the skin are seldom serious unless secondary infections arise through scratching of the lesions

The dermatitis is similar to the so called *swimmers' itch* caused by the penetration of nonhuman schistosomes in many parts of the world including the northern United States (Cort 1928) Barlow (1936) applied water containing cercariae of *S mansoni* to the skin of 8 persons already infected with this species and found that an itching sensation began in all cases in from 1 to 6 minutes There was considerable variability as to how severe the itching finally became but in most cases it became more intense after a few minutes Soon after application the area became swollen and red The swelling subsided later leaving a papule at each point of entrance An extensive dermatitis is frequently seen on the legs of men who sit in the water working a hand pump for purposes of irrigation The reaction subsides in a few days unless there is a secondary infection

When situated in their normal habitat in the veins of the mesenteric plexus **the adult worms** cause *very little direct pathologic damage Occasionally they* incite reactions in the walls of the veins and especially in the case of dead worms the veins may become obliterated These reactions appear to be rare *however and their significance is relatively slight in comparison with the* other types of damage usually seen in the same cases When the worms are located in unusual situations they are often the cause of much more obvious *damage Only in the lungs do such reactions occur at all frequently The* possibility that occasional young worms return to the lungs after starting their growth in the liver and complete their growth in the pulmonary tissues has *not been thoroughly investigated Most cases with pulmonary infections how*ever are well advanced cases with severe liver damage making possible the passage of adult worms into the pulmonary circulation through anastomoses *between the portal system and the radicles of the hepatic vein The constrict*ing periarteritis about these worms may gravely impede the pulmonary circulation with consequent strain on the heart (Day 1937) These conditions are *generally preceded however by severe pathologic damage in other organs* and the patients already have a very poor prognosis

Most pathologists who have made an intensive study of schistosomiasis believe that either **toxins** *secreted by the worms or* ***metabolic products*** *of the* worms play a large part in this disease No specific toxins have been isolated however and there is no experimental evidence bearing on the effect of any particular *metabolic products The argument in favor of such action is sup*ported almost wholly by the fact that other explan ... of the observed pathologic processes do not seem t ... icient The ... ptoms which arise early in the disease resembl ... *ly certain* ... mias Some of the tissue changes in the liv ... ult in ... ilar outlines and a granular endoplasm are ou ... ortion to ... al ... age and suggest to Fairley (1920) *tl* ... alized ... toxic action K ... 1941) a ... is a p ... toxin using this ... sense ... or ... of the adult wor ... *infl* ... are ... even in mild ... fib ... nly ... but is diffuse eve ... are

focal fibrosis caused by inert substances. Girges (1934) presents a long list of what appears to him to be the effects of toxins. Many could be explained in other ways, but even where there seems to be no other plausible explanation no direct evidence is presented. Other similar observations support the case for toxic substances, but there is obvious need for further experimental work in this field before definite conclusions can be drawn.

By far the greatest amount of damage is attributable to the effects of the eggs extruded from the blood vessels into the tissues. Whether these act merely as foreign bodies or secrete a toxic substance remains somewhat in doubt. With few exceptions the early reaction of all tissues is more or less the same and typically involves the formation of a pseudotubercle about each egg. The later reactions, however, are more variable and depend on the nature of the organ involved.

The mechanism by which the eggs pass through the walls of the blood vessels has been studied extensively, and in the discussion of this problem greatly divergent opinions have been expressed. The most recent extensive observations have been made by Kohlschutter and Koppisch (1941), who have summarized the opinions of previous investigators. Their own observations were made on experimental animals and confirmed by a study of pathologic material from cases in human beings. They describe the extrusion of eggs from the venules as follows. The egg first adheres to the lining of the vessel; then endothelial cells begin to grow over it from all sides until it is completely covered. At this stage the original endothelium is still clearly visible between the egg and the tissues. Then the endothelium grows over the egg, leaving it outside of the vessel wall. Except in the intestinal mucosa, this stage is followed by leucocytic infiltration and later by proliferation of fibroblasts and histiocytes with the formation of a pseudotubercle. If the number of eggs in the vicinity is few, there is no interruption to the blood flow, as the blood vessel is merely pushed aside. Where groups of eggs were found together, however, it was observed that the flat cells in continuity with the endothelial lining extended between and over adjacent eggs forming a network. Although in this case the process led to localized obliteration of the vessel, thrombosis was never encountered. In the mucosa the formation of pseudotubercles is rare. Here the eggs are similarly extruded by an overgrowth of the endothelium, but there is no appreciable accumulation of fibroblasts or histiocytes. The authors state that the eggs which are extruded into the mucosa are virtually the only ones which reach the lumen of the intestine, but they do not give any clear description of the process after the eggs are in the tissues.

Previously, the opinion has been that the spine is a mechanical aid in the passing of the eggs through the wall of the venule and through the tissues, but Kohlschutter and Koppisch find no evidence that the spine plays any part in the extrusion of the eggs other than causing them to adhere more readily to the wall of the blood vessel. Moreover, they are convinced that there is no evidence of toxic or histolytic secretion from the eggs as Hoeppli (1932) believed. The observations of Kohlschutter and Koppisch on the mechanism of extrusion of the eggs have been confirmed by Torres and Pinto (1946),

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except that these latter authors also ascribe certain features in the appearance of the tissues to toxic secretions from the eggs

The formation of the pseudotubercle is similar in all tissues and has been described by many authors Fairley (1920), in his account of studies on experimental infections in monkeys and observations on material from human beings, notes that the pseudotubercle appears grossly as a small whitish nodule varying in size from 0 5 to 4 mm in diameter His observations on the cellular layers involved in the pseudotubercle have been confirmed in all essential aspects by various pathologists The most detailed descriptions are probably those given by Koppisch (1941, 1943) which are illustrated with excellent photomicrographs of all the developmental stages He records the size of the



Fig 358 —Schistosomiasis mansoni section of epiploic appendage of the colon showing pseudo tubercles (Courtesy of Horace I Giffen)

spherical fibrous nodule which ultimately forms from the pseudotubercle as averaging from 200 to 250 microns in diameter The earliest reaction about the eggs in the tissues is an accumulation of eosinophiles Rarely these are accompanied by polymorphonuclears and in a few cases, only the latter are present If the miracidium has already died and been absorbed lymphocytes are the first cells to appear The next response is the formation of one or more foreign body giant cells By this time the miracidium has almost always disappeared and is replaced by either coagulated serum a few eosinophiles or a giant cell The next stage is the development of a zone of epithelioid cells which resemble those of tubercular granulomas enclosing the egg and the giant cells Around this zone there is an infiltration of the following types

of cells in variable proportions listed in order of their frequency and abundance lymphocytes eosinophiles monocytes and plasma cells

At this stage the developmental stages become regressive There is a concentric proliferation of fibroblasts among the cells surrounding the zone of epithelioid cells These fibroblasts begin the formation of a capsule at first broad and loose but gradually becoming more compact and dense With the development of collagenous fibers and the shrinkage of the fibroblasts the epithelioid zone becomes narrower the giant cells become smaller the leucocytes disappear from the center and are reduced in the peripheral zone Finally the lymphocytes disappear and the epithelioid cells are replaced by fibrous tissue from the capsule All that remains is a sharply outlined fibrous nodule with an egg shell and one or more shrunken giant cells in the center and a few lymphocytes about the periphery In the course of time the cellular elements disappear the egg shell undergoes fragmentation or total dissolution and the healed pseudotubercle is merely a fibrous nodule in which only a few small nuclei of fibroblasts are to be seen The pseudotubercles do not show necrosis in the center except in very rare instances Koppisch (1941) states that these cases with necrosis are associated with active infections and he believes that the process may be due to an allergic reaction provoked by the killing of large numbers of worms by treatment

The pseudotubercles are found in nearly all organs and tissues in which the eggs occur but they are most numerous in the liver They are not so frequently found in the intestine and Koppisch believes that many eggs are destroyed by the action of leucocytes and giant cells disappearing without leaving a trace of healed nodules In some cases however the pathologic process in the intestine is initiated by the formation of pseudotubercles proceeding to a chronic inflammation and resulting in granulomatous masses often simulating tumors and occasionally complicated by the development of malignancy (Giffen 1945)

The pathologic changes in the intestinal tract are usually confined to the rectum sigmoid and descending colon When there is a massive infection the effects are seen at higher levels perhaps because crowding causes the worms to distribute themselves over a wider area Since the active lesions in the more chronic cases frequently tend to be higher up the intestinal tract Koppisch (1941) suggests that the worms may be induced by the inflammatory changes in the lower bowel to move to higher levels The most characteristic reaction is a marked colitis which may either be extensive or may involve only small areas There are marked congestion and edema of the submucosa and usually a mild inflammatory reaction in the mucosa The mucosal surface is often described as having a granular or nodular appearance like sandpaper which is caused by the reaction around the eggs Sometimes these nodules may erupt into the lumen but more often portions of the mucosal surface slough off as part of an extensive ulceration process Bercovitz et al (1944) have noted that on proctoscopic observation these ulcerated areas are noninflammatory in appearance and give the impression that something has been extruded from beneath Of those seen on one day many had disappeared

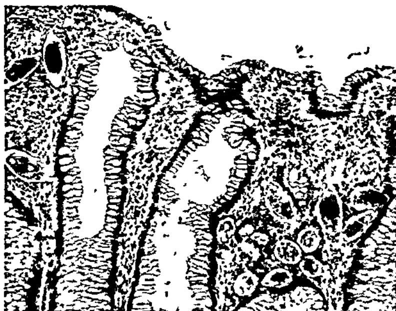


Fig 359.—Schistosomiasis mansoni section of intestinal wall showing inflammation of the tissues about the eggs (Courtesy of Horace K Giffen)

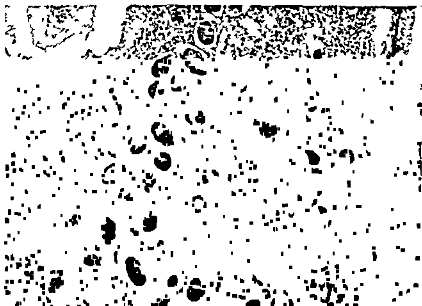


Fig 360.—Schistosomiasis mansoni section of intestinal wall showing granulation tissue around the eggs (Courtesy of Horace K Giffen.)

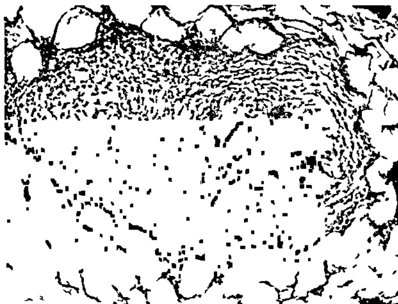


Fig 361—Schistosomiasis mansoni Section of granuloma around eggs in the omentum (Courtesy of Horace K Giffen



Fig 36 —Prolapsed anal polyp typical of those frequently seen in schistosomiasis mansoni Courtesy of Horace K. Giffen)

on the next Hutchison (1928) believes that schistosomiasis has no inherent capacity to produce ulcerations, a conclusion confirmed by other pathologists working with post mortem materials He notes that the swollen, hyperplastic mucosa abrades easily, and attributes the ulceration to secondary bacterial infections He has observed that the abscesses are superficial and that granulations develop in the ulcerated area at once Manson Bahr (1945) and Jaffé (1939) mention the frequency with which this condition is *complicated with* amebiasis In advanced cases the granulations may become extensive, forming tumorous masses Complicating carcinomatas may be stimulated by this extensive reaction if it is continued through many years, as they *seem to*



Fig 363 —Section of hemorrhoidal polyp containing eggs of *Schistosoma mansoni* (Courtesy of Horace K. Giffen)

occur more often than would be expected from chance association Adeno papillomata frequently occur and in heavy infections may appear quite early, Fairley (1920), for example having found them in the colon of monkeys 10 or 12 weeks after infection He describes them as massive cellular accumulations of the submucosa bulging the mucosa into conical elevations There is excessive proliferation and downward invasion of the glandular tissue of the mucous layer, but the core is always composed of submucosal tissues Rectal polyps *are often seen and sometimes* protrude from the anus in the form of hemorrhoids These polyps produce an uninterrupted urge to defecate, and

Hutchison (1928) believes that the constant strain which results is the cause of the relaxation of the perineal muscles edema of the gut and prolapse of the intestine occasionally seen in this infection

Even in Egypt where these severe manifestations have been most often described they occur in only a small proportion of the cases Jaffe (1939) believes that they are even rarer in Venezuela but the relative difference is probably more apparent than real since the Egyptian physicians see millions of cases in the extensive system of government hospitals (Scott 1942) On the other hand Jaffe found that systematic microscopic examination of material from unselected autopsies reveals many infections in persons with no noticeable symptoms In this connection Bercovitz et al (1944) report that on proctoscopic examination of 100 Puerto Rican army recruits with asymptomatic infections small ulcers were seen in 94 They were either pinpoint and only a few millimeters in diameter or linear and less than 3 mm long They were sharply demarcated from the normal mucosa nearly always lay directly over the capillaries and were situated below the rectosigmoid fold These authors conclude that there is no such thing as a healthy carrier and that a large group of cases with active lesions but no symptoms has not been given due consideration Koppisch (1941) and others have pointed out that a large number of autopsies of persons dying from unrelated causes show minimal lesions of unsuspected schistosomiasis

As the cases become more **chronic** there seems to be a tendency for the intestinal reactions to decrease in severity while the lower bowel often becomes fibrotic and narrowed The active lesions may not entirely disappear but when they do occur they tend to be located at higher levels The fibrotic changes may extend to the mesenteries and affect the lymphatic glands and other abdominal tissues

By far the most serious pathology and that which most often leads to death is the development of **cirrhosis of the liver** Koppisch (1941) emphasizes that the intestinal and hepatic pathologic processes both begin early in the history of every infection but they develop at different rates and lead to the erroneous conclusion that they are sometimes mutually exclusive Fairley (1920) first described the development of the cirrhosis in monkeys confirming the observations on material from human beings He also pointed out that this process begins early in the infection with the deposit of only a few eggs although the symptoms do not appear until much later when the process has become advanced The eggs pass from the blood vessels into the liver tissue just as they do in the intestine The early reactions are those involved in the formation of pseudotubercles The stages in the development of the cirrhosis as described by Fairley are first the appearance of fibroblasts dividing the eosinophiles into separate masses second the appearance of newly formed capillaries third the isolation of islets of hepatic cells with nuclei massed together so as to resemble giant cells Capillary congestion may be sufficient to lead to compression of the hepatic parenchyma It has already been pointed out that other tissue changes suggested to him that the final result depends

not alone on the mechanical effects of the accumulation of eggs in the liver but that a toxic action would appear to be involved

In endemic areas where reinfection occurs and the eggs continue to be deposited for many years the cirrhosis eventually leads to the pipe stem type originally described by Symmers (1904) He first noted the concomitance of schistosome eggs and this type of cirrhosis in which sections through the liver showed elongated white masses resembling ' white clay pipe stems' thrust at angles through the liver These masses were the result of an enormous increase in the fibrous tissue of Glisson s capsule surrounding the portal canals They appear porcelain white or occasionally pinkish and when cut they can be seen to contain the blood vessels and bile ducts The portal obstruction accompanying the cirrhosis results in the development of a collateral circulation often complicated by the formation of esophageal varices which not infrequently give rise to fatal hemorrhage

The **endemic splenomegaly** which is common in some parts of Egypt is now considered by most authorities to be caused by schistosomiasis mansoni There has been much prolonged discussion on this matter and even yet unanimity of opinion is not complete There seems to be little question about splenomegaly occurring as a result of schistosomiasis The geographic distribution of the endemic form exactly paralleling the distribution of *S mansoni* in Egypt seems to be good evidence in the case As to the mechanism by which the splenomegaly is caused there is less unanimity of opinion Most pathologists believe that the characteristic splenomegaly associated with severe cases of schistosomiasis mansoni results from the production by the cirrhosis of an increased blood pressure in the splenic vein Onsy (1937) however has studied 14 000 cases of splenomegaly and believes that the enlargement results from a response of the reticuloendothelial system to deposit of eggs in the spleen Although the eggs do not often appear in microscopic sections of the spleen in most cases of splenomegaly egg shells can usually be obtained by the digestion of reasonably large portions of the splenic tissue Onsy contends that the eggs are rapidly disintegrated and that repetition of the process leads to the permanent hyperplasia and fibrosis ordinarily seen and that the enlargement does not depend on either the intestinal or the hepatic lesions as believed by other workers Cases have been reported in which there is a pronounced splenomegaly without a corresponding enlargement of the liver but as a rule the cases with splenomegaly also show a pronounced cirrhosis

Girges (1932) has presented a theory that in the so called visceral types of this disease i e in cases with cirrhosis and splenomegaly the infection consists exclusively or predominantly of male worms That such a situation could occur is clear from the fact that all cercariae developing from one miracidium are of one sex Girges does not anywhere present his data in the form of protocols but merely states that he has found predominantly male worms in a number of such cases His evidence has not convinced most authorities in the field Experiments with unisexual infections in animals (Jaffe et al 1945) have not entirely clarified the situation and an open mind should undoubtedly

be preserved in the matter The evidence at present appears to indicate that the changes in the liver are due primarily to deposit of the eggs and the splenomegaly occurs as a secondary phenomenon produced by the changes in the liver and the portal circulation

If the severe cases progress beyond the point where treatment can arrest the pathologic process they may ultimately develop very large spleens Some have been reported as large as 7 or 8 kilograms while Girges (1934) notes that the spleens in the majority of his cases of splenomegaly are about 2 kilograms in weight Unless these cases are terminated by hematemesis from the esophageal varices or by other acute episodes a severe ascites can be expected to appear as a terminal phase of the so called visceral schistosomiasis

The primary effects of schistosomiasis mansoni on organs other than the intestine liver spleen and associated structures are by no means rare but as part of the over all picture they are seldom of major importance The eggs occasionally are found in nearly any organ or tissue and the reaction caused is usually typical of the reaction of the particular tissue to foreign bodies The pulmonary complications of the disease have already been mentioned and the secondary effects of these complications on the heart considered Jaffe (1940) has found evidence of myocarditis in many more cases of schistosomiasis than would be expected from the reports of previous work The eggs are only rarely found in the myocardium and he postulates a circulating toxin as the important etiologic factor Animal experiments (Jaffe et al 1945) have tended to support his observations of the occurrence of infiltrations in the heart muscle associated with this infection but further work will be needed before this phase is clearly understood The localization of eggs in organs such as the brain is very rare in any case but is less common in schistosomiasis mansoni than in schistosomiasis haematobia Papular lesions of the skin from which schistosome eggs have been aspirated have been reported by Black (1945) and other authors In nearly every case the effect of eggs in these unusual locations is unimportant as compared with the primary effects in the intestine or liver of the same case

In all of the tissues reacting to schistosomiasis there is a characteristic deposit of brown pigment which appears to be hematin and is indistinguishable from that found in cases of malaria It is therefore of diagnostic value only where malaria can be ruled out and other evidence of the presence of schistosomiasis is found In cases which have been thoroughly treated and all the worms killed and where no reinfection has taken place the pigment eventually disappears from the tissue

CLINICAL SYMPTOMS

The first symptoms seen in infections with schistosomiasis are those associated with the dermatitis resulting from the penetration of cercariae described above In most people where infections are acquired slowly the dermatitis is not differentiated from insect bites and other causes of itching papules In the case of persons whose occupation requires constant exposure

such as the Egyptians who sit in the water turning a hand pump the dermatitis becomes massive and is definitely associated in their minds with the exposure Persons newly arriving in an endemic area have often exposed themselves by swimming and have developed a severe dermatitis identified from the history as a *schistosome dermatitis* *The itching usually persists for only* a day or two and all traces have disappeared within a few days unless a secondary infection is induced by scratching

After the dermatitis has subsided no further symptoms are noticed in most persons for some time In some cases there are symptoms arising within the first few weeks Although other authors have mentioned these prodromal symptoms Pons (1937) was probably the first to differentiate them clearly from the acute toxemia which usually ends the incubation periods These prodromal symptoms include anorexia nausea vomiting slight abdominal pain mild diarrhea extreme fatigability and malaise

Except for the few cases in which prodromal symptoms are recognized the incubation period usually ends with a sudden onset of fever introducing the acute toxemia stage The time of the onset after the original infection varies according to different authors from 3 to 8 weeks although some may have included the prodromal symptoms in their time limit Pons calls attention to the fact that the onset in many cases is in the sixth or seventh week which is about the time when the worms can be expected to have matured migrated into the mesenteric veins and begun to deposit eggs A reasonable explanation seems to be that the symptoms are some type of allergic response to stimuli produced by the eggs or maturing worms The fever may be remittent or intermittent or it may sometimes run a fairly level course In many respects the condition often closely resembles typhoid fever In addition to manifestations ordinarily associated with febrile conditions there are gastrointestinal symptoms of various types varying from mild discomfort and distention to abdominal pains nausea vomiting diarrhea or dysentery These *symptoms may be accompanied* by an urticaria or a dry persistent cough Frequently there are tenderness and enlargement of the liver and a congestive enlargement of the spleen In cases with coughs physical examination may show patchy areas attributable to a bronchopneumonia which Koppisch (1943) suggests may result from the migration of worms through the lungs

In persons residing in endemic areas it is seldom that the early symptoms of schistosomiasis are differentiated from those caused by other infections These symptoms for the most part have been described in persons who have entered an endemic area for the first time where there is a clear history of bathing in infected water to point to the connection between the symptoms and the infection There has also been sufficient work with experimental animals to indicate that this connection is valid It is not clear whether people who reside in endemic areas and receive successive light infections from early childhood fail to show the acute early symptoms or whether *they merely fail to report* them Girges (1934) working in the heart of a severe endemic area saw early symptoms in 0 3 per cent of his cases He does not mention whether or not these were town dwellers whose first exposure might have been relatively

late in life and heavier than the average Hutchison (1928) and Pons each record a case with pronounced early symptoms following a return to the endemic area after an absence Most of the cases whose early symptoms have been studied have apparently received relatively massive infections Nearly all of them received treatment and the febrile stage ended after 2 or 3 weeks Pons records 1 case where specific diagnosis was established only on the forty ninth day of fever and another case without specific treatment whose fever virtually disappeared soon after the twenty ninth day

Differential diagnosis at this stage must consider brucellosis typhoid fever, and malaria as well as the possibility of pulmonary tuberculosis where there are physical signs in the lungs Leucocytosis and eosinophilia are of some help although the latter may be expected in nearly any person living in an area where helminth parasites are common The finding of schistosome eggs in the stools is of course indicative especially if the stools are negative when the febrile condition begins and become positive later

After the acute symptoms of the initial period have subsided there is usually a long time before any symptoms are again noticed There is a great variability between persons with regard to the length of the symptom free period and the severity of symptoms when they again occur This variability is most likely associated with the number of worms acquired and the frequency and extent of reinfection Some persons probably never show any further symptoms (Girges 1934) In this connection the above mentioned studies of Bercovitz et al (1944) should be recalled in which a large proportion of symptomless cases showed intestinal lesions Other patients do show at this time symptoms referable to the pathologic process known to be proceeding in the intestinal wall These symptoms vary from mild abdominal discomfort and mild intermittent diarrhea to a pronounced dysentery often alternating with constipation and in many cases accompanied by the occasional or frequent appearance of blood in the stools

The classification of cases into 2 distinct types the intestinal and the hepatic, in which Girges (1932) has been followed by many clinical writers has already been discussed Pons (1937) believes that patients are differentiated early in the history of infection into those who are destined to develop an intestinal type of pathology and those whose pathology will be primarily hepatosplenic On the other hand Fairley (1920) showed that the initial phases of the cirrhotic process begin soon after infection even though the symptoms do not appear for a long time Koppisch (1941) presented evidence to support his contention that the disease is both hepatic and intestinal in its fundamental pathology from the very beginning in all cases and that the liver symptoms merely appear at a much later date than the intestinal by which time the intestines may have become so fibrotic that no symptoms remain in evidence Useful as the classification may have been for purposes of discussion it now appears that the differences are those of timing and degree rather than of kind The evidence now available indicates that the so called types should be looked upon as two phases in the same pathologic process either of which may receive emphasis in any particular case

During the intestinal stage of the infection, cases with a severe anemia have been described, but such cases usually represent a small portion of the series under study Rodríguez-Molina and Pons (1936) studied 8 cases, 3 of which showed an anemia at this stage, but 2 of these were known to be on an anemia inducing diet The loss of blood in the stools may account for the anemia in some cases, and in others there may be some type of derangement of the hematopoietic function As yet no definite etiologic connection between the anemia and the schistosomiasis has been established, and it seems doubtful if, in a cross section of typical cases, anemia can be considered a consistent manifestation The author made hemoglobin determinations on several hundred people representing a typical cross section of an Egyptian village where there was a high prevalence of *S mansoni*, *S haematobium*, hookworm, ascaris, and other intestinal worms Because of this high prevalence, clear cut conclusions were not possible However, statistical analysis showed that hookworm disease in these people was definitely associated with anemia in proportion to the severity of infection, but there was no such association between anemia and infection with either species of the schistosomes

Diagnosis during the early intestinal phase of the disease is usually relatively easy since this is the stage of rapid egg deposit Persistent examination of the stools should reveal the eggs in nearly any case at this stage Treatment is especially indicated during this phase to prevent the infection from going on to more serious conditions, but differential diagnosis should not be neglected, since amebiasis or some other more acute condition may deserve prior attention Biggam and Arafa (1930) recommend that the sigmoidoscope be used in differential diagnosis, and present some excellent colored plates of the lesions encountered in schistosomiasis Prognosis is good where adequate treatment can be administered at this stage In fact, for most patients the real danger lies in the later development of cirrhosis

In untreated cases the fibrosis developing as the infection becomes more chronic, seems to reduce the symptoms associated with the colitis In these chronic intestinal phases the passage of eggs into the lumen tends to be reduced, and diagnosis becoms more difficult A small proportion of the cases develop a serious intestinal pathology either prior to the appearance of manifestations of liver damage or at the same time that these become evident The most frequent symptom in these severe cases is dysentery, which often is intermittent and may alternate with constipation Rectal polyps, especially those of the hemorrhoidal type, are a frequent cause of complaint In a few cases where the pathologic process in the intestine has become advanced before receiving any medical attention portions of the thickened and relaxed intestinal wall may prolapse For a time the patient may be able to reduce the prolapsed portion after he goes to stool but often a permanent prolapse results, some times involving the entire rectum Anal fistulae and fissures are seen in a large proportion of the advanced cases Anemia is often present, especially if the person has suffered from loss of blood for a prolonged period

As a rule patients seeking treatment for the first time during the intestinal phase come because of their weakness and inability to do a day's work

They may come earlier when their symptoms are primarily anorexia nausea flatulence and distress after eating. On examination during this phase the colon feels thickened and hard on palpation and the liver and spleen are usually somewhat enlarged. Except for the extreme conditions such as prolapse extensive papillomatous growths and complicating malignancies prognosis in the advanced intestinal stage depends primarily on the condition of the liver and is reasonably good unless the symptoms of cirrhosis are also pronounced.

The cases which are seen for the first time after the cirrhosis is well advanced have been classified as the visceral or hepatic type. As mentioned above, the changes in the liver apparently always begin early in the course of infection but it usually is a long time before the symptoms arise probably as much as 10 years in many cases. It is doubtful if any cases reach the stage of cirrhosis without displaying intestinal phenomena although these may have been so mild that the patient did not associate them with schistosomiasis thus making it impossible to obtain a clear history. Most of the cirrhotic cases either show intestinal symptoms or have a fibrotic colon as evidence of previously active intestinal lesions.

The symptoms which are seen during the visceral stages of the disease are extremely variable depending on the degree of advancement of the cirrhosis. The liver enlarges for several years as the cirrhotic process advances then as fibrosis becomes prominent it shrinks and in the later stages may have receded beneath the costal margin. Colitis may still be the predominant feature as far as the patients subjective symptoms are concerned but more often the patients come to the attention of the physician at this stage because of vague abdominal symptoms nausea tenderness and pain in the abdomen. Most often they complain of a weakness which prevents them from working and a feeling of weight in the abdomen. The liver may be moderately or greatly enlarged and is frequently tender. The spleen is usually somewhat enlarged but not tender. In cases with marked splenomegaly the patients complaints usually have to do with the weight of the mass and abdominal distention. The eosinophilia usually but not always persists through this stage and a leucopenia is characteristic. The anemia which is so frequently associated with schistosomiasis at this stage cannot be definitely attributed to the effects of this disease. Deficient diets and other conditions leading to anemia are always common in the regions where this disease is endemic. The later stages of cirrhosis usually produce an ascites after which life is usually measured in months according to Day and Ferguson (1909).

Diagnosis during the cirrhotic stage is usually relatively easy although a fairly long search may be necessary before eggs can be found. Methods involving removal of eggs directly from the intestinal mucosa may be required. In the cases where eggs cannot be found immunologic tests may be of some value but diagnosis depends primarily on symptoms and history. Differential diagnosis is always important especially as regards the elimination of other forms of cirrhosis and other causes of splenomegaly. The clinical picture

often exactly duplicates that of Laennec's cirrhosis and the splenomegaly does not differ from that seen in other conditions originally included in Banti's syndrome

Prognosis with treatment depends upon the extent to which the cirrhosis has developed The frequently associated colitis can be healed and if the liver damage has not gone too far a reasonable degree of health may be re established in the absence of reinfection Treatment will not arrest a well advanced cirrhosis however nor will it reduce splenomegaly In young persons splenectomy is often successful

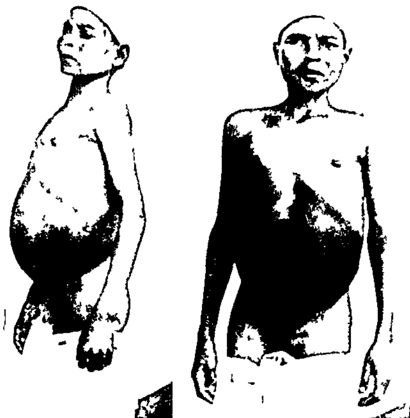


Fig 364 —Splenomegaly in young Egyptian who regained his health after splenectomy Spleen weighed 1 780 grams after it had been reduced in size at operation by first clamping splenic artery and allowing blood to drain back into the circulation The liver was only slightly enlarged (Courtesy of Horace K Giffen) (For further description see Giffen 1945)

Not infrequently the terminal phase involves hematemesis resulting from the esophageal varices already described Terminal pneumonia and other pulmonary disturbances are to be expected Some of the latter may be attributable to the eggs and worms which are often found in the lungs after anastomoses are established in the liver between the portal circulation and the tributaries of the hepatic vein Symptoms of dilatation and other cardiac irregularities are often seen in the later stages but seldom predominate in the

whole clinical picture There is no agreement among pathologists as yet as to whether the myocarditis which has been demonstrated in many cases and in experimental animals is primarily due to toxins from the worms as believed by Jaffe (1940) Meira and Ramos (1944) state that except for the rare cases characterized by the presence of schistosome granuloma in the myocardium the cardiopulmonary type of cases seldom show electrocardiographic changes not attributable to other conditions Until more cases have been studied no conclusion can be drawn These authors note especially the need to differentiate from Chagas' disease at the stage of cardiopulmonary symptoms The cirrhotic process itself brings about the death of many cases and most pathologists would probably agree that the cause of death in the vast majority of cases is *fundamentally referable to the cirrhosis of the liver*

LABORATORY FINDINGS

In suspected cases of schistosomiasis the first evidence to be sought is the presence of eggs in the stools In regions of high endemicity the eggs will be *found in the urine of about 15 per cent of the cases* *Providing the feces* are examined only by one of the usual routine methods about one third of those with eggs in the urine will not show them in the feces (Scott 1937b) Examination of the urine in cases where the eggs are not easily found in the feces is warranted by the greater ease of examining the urine The eggs are readily found in the sediment from at least 50 c c of urine after it has stood 30 minutes in a *conical sedimentation jar* *The first morning specimen and the* last portion of any passage are apt to have more eggs than unselected specimens Spreading the sediment on a microscope slide ringed with a greased pencil and allowing it to dry (Barlow 1931) provides a permanent preparation which can be rewet and examined repeatedly Slides so prepared and kept by the author in ordinary slide boxes subjected to extremes of climatic conditions for 12 years are still in good condition The drying urine apparently acts as a preservative It is even possible to see that the miracidia in some were intact and presumably viable at the time of drying Studies made at the time of preparation showed that eggs killed before passage by treatment with antimony do not present this appearance but are either dark or filled with disintegrated materials

In examining the feces a simple smear as prepared for the diagnosis of intestinal parasites is seldom used for this species Most reports refer to selected smears made from bits of mucus or blood seen on the surface of the stool Such smears will reveal eggs in a large proportion of the cases probably about 50 to 80 per cent depending on the intensity of infection in the area (Tomb and Helmy 1931) When a dilution egg count is being made for other purposes the results can be substituted for those obtained by smears since each egg count slide will reveal eggs about as efficiently as each selected smear, for example in a series of stools known to contain eggs they were revealed by 1 egg count slide in 67 per cent and by 3 slides in 84 per cent each slide containing 1/200 c c of feces (Scott 1937a) Unless egg counts are al

Fuadin and tartar emetic, there is still some dispute as to which is superior with regard to effectiveness or toxicity The choice between them is usually made on grounds of cost or convenience In the hands of private physicians, Fuadin has nearly everywhere replaced tartar emetic Its stability makes it possible to keep it on hand *in ampules The slightly shorter course of treat* ment and the fact that it can be given intramuscularly rather than intra venously are practical points in its favor On the other hand, tartar emetic is much cheaper than Fuadin and it is, therefore, still being used where cost is a factor, as in large scale treatment campaigns where pharmacists are avail able to keep freshly prepared solutions on hand

Tartar emetic must always be given intravenously with precaution against even a slight amount coming in contact with the tissues because of its local irritating effects, producing necrosis and sloughing The recommended course of treatment varies somewhat, the following schedules being rather extreme examples According to the latest report received before the war, the Egyptian government was treating approximately 500,000 patients a year as it had for many years according to the following routine (Khalil, 1931) Intra venous injections of tartar emetic in 6 per cent aqueous solution are given on alternate days 3 times a week for 4 weeks The following doses are for adults weighing 60 kilograms or more and to be reduced proportionally for those weighing less The doses during the first week are 0 5 c c , 1 0 c c , 1 5 c c , thereafter each dose is 2 0 c c The doses are reduced if marked signs of tox icity occur If not, and if viable eggs are still being passed after these 12 injections 3 additional injections of 2 0 c c are given The course recom mended by the U S Army (Anon , 1945) recommends intravenous injections of a 0 5 per cent solution of tartar emetic in saline or distilled water given on alternate days, the first adult dose is 8 c c and subsequent doses are in creased by 4 c c until the dose reaches 28 c c This dose is maintained until a total of 15 injections have been given The total amount of drug given by this regimen is thus only slightly greater than the amount given in the total 15 injections of the former method The injections are always given slowly, and usually with the patient recumbent, although in Egypt the patient is treated in a sitting position and is allowed to walk immediately into another *room, where he is required to remain sitting or lying for a period of 2 hours.* Many physicians feel that, for the greatest safety, the patient should be hos pitalized during the course of treatment, or at least kept in bed from the time of the injection until the following morning Nausea, vomiting, and cough ing frequently occur soon after the injections are given, but are not consid ered by most authors as signs of toxicity sufficient to warrant discontinuing the treatment A number of fatalities have been reported each year as a re sult of treatment in Egypt, but some are not reported, and Khalil believes *the true figure* to be about 1 in 2,000 receiving the full course Contraindica tions are cardiac disease, fever, advanced cirrhosis, nephritis acute pyelitis or any other serious kidney condition In pregnancy the patient should be hos pitalized

Fuadin is supplied in ampules containing a 6 3 per cent solution which is given intramuscularly on alternate days or 3 times a week The dosage usually recommended is 1 5 c c for the first 3 5 c c for the second and 5 0 c c for succeeding doses to a total of 9 doses The U S Army recommends (Anon, 1945) that this series be extended to 16 doses so as to equal the antimony content of the tartar emetic series In any case, if viable eggs are still being passed a week later, 5 more injections are usually given Khalil considered the above dose as applying to a person weighing 60 kilograms and reduced the dosage for children proportional to the weight Hernandez Morales (1945) recommends a slightly higher dosage for children giving 0 5 c c for the initial dose, and if no reactions follow 0 05 c c per kilogram of body weight for the second dose and 0 1 c c per kilogram of body weight for succeeding doses until about 1 0 c c per kilogram has been administered Coughing does not characteristically follow Fuadin but nausea, vomiting epigastric pain, pain in the joints and chest do occur Dizziness or marked signs of depression of the circulatory or respiratory systems are indications of toxicity calling for interruption of treatment or reduction of dosage Deaths have followed the use of Fuadin but the records are not sufficiently dependable to determine whether they are less frequent than after treatment with tartar emetic The contraindications are the same as for tartar emetic It seems probable, however that cases of cirrhosis will tolerate Fuadin better Salah and Hassan (1935) having found that cases with a disturbed liver function showed improvement in this respect after treatment

Recently there have been several trials with intensive treatment with these antimony compounds Alves and Blair (1946) injected slowly 10 c c of a 5 per cent solution of sodium antimony tartrate 3 times at 3 hour intervals on each of 2 consecutive days Mills (1946) used daily injections of Fuadin 6 days a week for 2 weeks Halawani and Abdallah (1946) used 5 c c of Fuadin per 60 kg of body weight 3 times at 3 hour intervals on 2 consecutive days Selected cases were used for trial to eliminate all persons with any possible contraindication Several hundred cases have been treated by these methods and, as far as can be determined the results seem to be about as good as with the standard courses No severe toxic reactions were seen and the mild signs were no more than are expected from the standard treatment The results are encouraging and should lead to further experimentation under carefully controlled conditions

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Fungi belong to the plant kingdom They are members of the Thallophyta filamentous plants with very simple cellular structure trast with higher plants they do not possess stem roots or leaves phyta include Algae and Fungi the Algae being differentiated from t by the presence of chlorophyll Fungi which lack this substance for of food lead a saprophytic or parasitic existence

Fungi are divided into Pseudomycetes and Eumycetes The first comprises the Schizomycetes or the *bacteria* and Myxomycetes simp Eumycetes are further divided into Hyphomycetes or imperfect fung imperfecti) so called because reproduction is not of the sexual typ mycetes which reproduce by ascospores Phycomycetes which repro means of zygospores and Basidiomycetes which reproduce by basid The last three groups have perfect or sexual reproduction From th point of pathogenicity the Hyphomycetes also called *fungi imper* the most interesting group

Fungi Imperfecti

Within the group known as fungi imperfecti are found mos pathogenic fungi Only these will be discussed They are classifie basis of their asexual spores varying greatly according to their mo and mode of living so that they present great difficulties in class They are grouped in genera on the basis of similarity of spore formatio than along phylogenetic lines although they are derived from differen types

With this information in mind as well as the practical purpos chapter we shall forego further reference to classification mention whatever is necessary for diagnostic purposes

Two kinds of structure are considered in the fungus the *vegeta* the *reproductive apparatus* The first enables the organism to obtain necessary for development The second is charged with reproductio organism

Vegetative Apparatus

The vegetative apparatus is formed by a multitude of filaments and interwoven in all directions which form the body This mat of is called the *mycelium* The individual filament is called a *hypha* *

The mycelium has been divided according to the diameter of its into the *macrosiphonate*, or large diameter and *microsiphonate* or ameter The first term denotes filaments broader than one micron ond filaments narrower than one micron Of those with the small c there is a group the Actinomyces † which is highly interesting with to pathogenicity The remaining pathogenic fungi have filaments w diameter

*Editor's note (O F) Common usage however refers to vegetative myc aerial mycelium the latter being the reproductive mycelium if spores are produced b

†Editor's note (O F Actinomycetales are classified as Schizomycetes by bact

No partition walls or membranes are observed in filaments with small diameter

The macrosiphonate mycelium may be continuous septate or budding The septate mycelium is formed by filaments joined like bamboo stalks The continuous mycelium lacks these joints The budding mycelium is formed by budding when the bud attains the dimensions of the original parent cell it sends forth *another bud thus forming a chain of elements which lengthens successively to* constitute the *pseudohypha* resulting in a *pseudomycelium* typical for the genus Candida and the colony is a soft yeast like colony

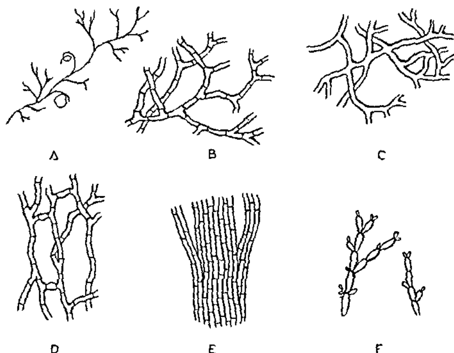


Fig 365—Various types of mycelia *A* Microsiphonate *B* macrosiphonate septate *C* continuous *D* anastomosing mycelium *E* mycelium in coremia *F* budding mycelium

The septate mycelium which is found more frequently has many subdivisions *coremiform* in which the filaments are grouped to form bundles *anastomosed* with branched filaments the branches *uniting* with each other *fuliginous* with a dark pigment etc These and other subdivisions not mentioned here will be explained in discussing particular characteristics of fungi later in this section

Reproductive Apparatus

The reproductive apparatus is composed of cellular formations called *spores* There are a number of types

1 **Thallospores**—Thallospores are *formed by the mycelium* or thallus Two types are found *Arthrospores* and *blastospores* The first are rectangu

lar cells formed by separation of the joints of a septate filament (fragmentation) Blastospores are formed by budding (gemmation) of a yeast cell

2 **Microconidia or aleurospore** *—Small rounded unicellular formations formed by condensation of protoplasm

3 **Macroconidia or fuseaux** *—In contrast to the above these are large fusiform cells with parallel transverse septa

4 **Conidia (true conidia)**—These spores are formed by a specialized hypha called *conidiophore* There is great variation in the manner in which they are grouped in relation to the hypha from which they originate in form color size etc

5 **Chlamydospores**—These are considered by some mycologists as thallospores Cells are formed by condensation of the protoplasm and enlargement They take a rounded form and develop a thick wall membrane They may start from the end (terminal) the middle (median) or the side (lateral) of the filament They are resistant spores

6 **Sporangiospores**—Globular sac like formation (sporangium) contains a multitude of small spores

These spore formations given here are the principal microscopic structures used as guides in a determinative study of fungi imperfecti

BASIC FACTS CONCERNING MYCOLOGIC TECHNIC

The technic and culture media used in the study of mycology differ from those used in bacteriology Pathogenic fungi with certain exceptions (*A bovis*), grow at room temperature In practical work simple media containing glucose and with a peptone base such as Sabouraud s medium are used In contrast to bacteria fungi require incubation for several days generally a week for their development

A variety of pathologic material may be obtained for the diagnosis of mycoses although generally the material is taken from the cutaneous surface It includes scales fragments of nails hair crusts pus from microabscesses etc In deep seated mycoses pus from nodules or abscesses sputum in cases of pulmonary mycosis cerebrospinal fluid etc are needed

Direct examination of a fresh specimen of the pathologic product is of great importance in mycology For this purpose use 20 per cent potassium hydroxide or Amann s chlorolactophenol to clear the material to be examined—hair scales nails If staining is considered double strength Lugol s solution is recommended as in the case of pus sputum etc

Smears should not be made since this procedure breaks up the mycologic elements making identification difficult

Success in results depends upon the selection of material for direct examination and for cultures Young lesions should be used In old or pre

*Editor's note (O F) Many authors use these terms only to designate the size of conidia

viously treated cases the number of parasites is decreased and they may not show in a direct examination, diagnosis then depends upon culture

Chlorolactophenol Amann.—

Chloral hydrate	2 parts
Lactic acid	1 part
Phenol crystals	1 part

Cotton blue, at a concentration of 0 5 per cent, may be added and gives a good stain for organisms in scales

Culture media used in mycology are varied In practice however, the glucose medium of Sabouraud with agar is sufficient to obtain culture of all pathogenic fungi with the exception of *Actinomyces bovis*

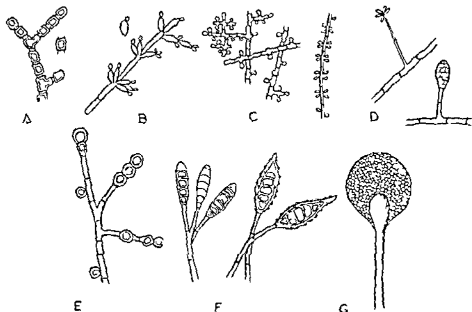


Fig 306—Asexual spores A Arthrospores B blastospores C aleurospores D conidia E chlamydospores F macroconidia (fuseaux) G sporangium

In our own practice we have used this medium as modified by Langeron (1943) It consists of decreasing the quantity of glucose to prevent pleomorphism or degeneration which some fungi undergo in culture particularly Dermatophytes with loss of the elements of reproduction (spores) so that only the vegetative mycelium remains

Sabouraud 2 Per Cent Dextrose Agar —

Water	1 000 c c
Dextrose	[illegible] *Gm*
Peptone	10 Gm.
Agar	[illegible] Gm

It is important not to oversterilize to prevent caramelization of the glucose*

*Editor's note (O F) For other media as corn meal agar etc. and standard lactophenol cotton blue stain see Gradwohl *Clinical Laboratory Methods and Diagnosis* ed 4 1948 Recently Littman's bile agar (Difco) has been used with excellent results in mycologic diagnosis as well as new media devised by the Baltimore Biological Laboratory

CLINICAL CLASSIFICATION OF THE MYCOSES

Diseases caused by fungi are classified into two large groups (1) superficial mycoses and (2) deep mycoses In the first group are comprised the common affections localized in the superficial part of the skin producing mild symptoms they do not endanger life and with few exceptions recovery occurs spontaneously Deep mycoses on the other hand invade structures underlying the skin and have a characteristic tendency to develop progressively and to terminate fatally in some cases

Henrici (1940) in analyzing the principal characteristics which differentiate superficial from deep mycoses pointed out certain considerations Superficial mycoses are of like character throughout the world deep mycoses show marked tendencies to restricted distribution, however they may become endemic Some few like sporotrichosis occur widely Blastomycosis of the American type appears to be limited to the confines of the United States Coccidioidomycosis practically exists only in certain states of the United States and in some states of the Mexican Republic The limited geographic distribution of deep mycoses has been explained by the fact that the fungi which cause these diseases are parasites requiring certain geographic conditions

With deep mycoses the course is similar to that of tuberculosis and leprosy Deep mycoses require introduction of the fungus into the tissues through trauma or inhalation they also require ability on the part of the fungus to survive and multiply in the sinuses of the tissues This does not result in any appreciable immunity so that there is no spontaneous cure The beginning of the disease is insidious The patient is not able to state the precise time of the beginning of his symptoms so that the disease may be in existence for several months before the individual considers it worth while to seek medical care Henrici (1940) represented the development of this type of mycosis by an ascending line very gradual at the beginning followed by accelerated velocity until it terminates almost vertically It would seem from this that the fungus is not capable of multiplying in the tissues in the beginning but that by its continuing presence in the tissues a change takes place either in the fungus itself or in its environment

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CHAPTER 49

SUPERFICIAL TROPICAL MYCOSES

Antonio González Ochoa

Superficial mycoses are lesions produced by various groups of fungi which attack the skin and its appendages the hair and nails In addition to the important and well known group of Dermatophytes there are others of less importance from the standpoint of pathogenicity which should be treated in detail because of their exclusive presence in the tropics or their major incidence in tropical regions

Among the important superficial tropical mycoses are trichomycosis vulgaris—black piedra—tropical mycoses due to dermatophytes tinea imbricata and little known tropical dermatomycoses pityriasis versicolor tinea nigra and keratomycosis nigricans palmaris tinea albigena

TRICHOMYCOSIS VULGARIS AND TROPICAL TRICHOMYCOSIS OF CASTELLANI

This affection described by Paxton (1869) has been called trichomycosis palmellina lepothrix trichomycosis nodosa etc Recent literature designates it also as trichomycosis axillaris

The large number of synonyms is due to the confusion which has existed about this disease According to Pignot (1936) trichomycosis vulgaris constitutes a chapter still open to study

DEFINITION

Trichomycosis vulgaris is an affection of axillary and pubic inguinoscrotal or vulvar hair characterized by the formation of small colored nodules which cover the hair and produced by a microsiphonate *Nocardia tenuis*

GEOGRAPHIC DISTRIBUTION

This mycosis is seen frequently in hot and humid regions although it is universally distributed

SYMPTOMATOLOGY

Upon the middle third of the affected hair there are most often yellowish nodules which are strongly adherent more or less numerous either spaced like beads in a rosary or confluent They do not invade the follicles The hair loses its color and becomes coarser and granular to the touch The concretions formed by the microorganisms embedded in a gelatinous substance may invade the cortex of the hair and develop beneath the superficial layer

This disease was redescribed by Castellani (1911, 1913 and 1922) under the name "trichomycosis tropicalis" in Ceylon the East Indies and Burma where it was quite common

Castellani (1911) explains that trichomycosis *tropicalis* differs from the *vulgaris* form in that the concretions in the hair in *tropicalis* are soft and easily detached He divided it into 3 varieties, *flava, rubra,* and *nigra,* according to the color of the nodules The yellow variety is caused by the parasite in its pure form and the other 2 in association with a micrococcus *M nigrescens* (Castellani 1911) for the black form and *M castellani* (Chalmers and Fairel 1915) for the red form

ETIOLOGY

The etiologic agent of trichomycosis vulgaris and trichomycosis tropicalis is a microsiphonate *Nocardia tenuis* Castellani, 1912 It is composed of slender filaments 1 to 1 5 microns or less in diameter and 4 to 10 microns in length These filaments are straight or slightly bent ramified gram positive, not acid fast MacFie (1916) reported that he had cultivated this organism on ascitic fluid agar obtaining translucent colorless colonies with opaque centers, with filaments 0 6 micron in diameter this has not been confirmed by other workers

Manson Bahr (1935) and Strong (1944) have recommended that the term "trichomycosis nodosa a name given by Patterson to trichomycosis vulgaris should not be confused with the term ' trichomycosis nodularis ' the name given by Juhel Rénoy to piedra Both authors use the names ' trichomycosis and "trichonocardiasis" when referring to nodosities produced by *Trichosporum beigelii* (Rabenhorst) Vuillemin 1902, the etiologic agent of the European white piedra causing confusion between trichomycosis vulgaris and white piedra

LABORATORY DIAGNOSIS

Affected hairs placed under the microscope, in Amman's chlorolactophenol or in potassium hydroxide solution show a collection of very slender, branching filaments resembling bacilli in chains embedded in a gelatinous substance These slender filaments of Nocardia are easily distinguished from the large thick walled cells of the agent of piedra

TREATMENT

Careful cleansing of the affected region and use of lotions of mercury bichloride in 1 1 000 concentration and 5 per cent iodates or 3 per cent resorcinol after shaving the area effect cure

BLACK PIEDRA

DEFINITION

The name piedra' is used to designate a disease of the hair and beard manifested by small hard nodules resembling pebbles adherent to the surface of the hair, and which invades beneath the superficial layer

Langeron (1936) divided piedra into 2 groups the white or trichosporic piedra and black piedra This connotation defines its principal clinical differential characteristic There is also a division into tropical Asiatic, and

European piedra however, this geographic division is not entirely apropos since European white piedra also exists in tropical regions and Asiatic black piedra is found in South America

According to Mackinnon and Schouten (1942), the etiologic agent of white piedra does not produce disease except of hair previously parasitized by other primary causes as black piedra trichorrhexis nodosa trichoptilosis

We shall deal with black piedra, an exclusively tropical affection White piedra will be discussed only for the purpose of establishing the differences between this disease and black piedra thus avoiding the confusion frequently encountered in these 2 conditions

Black piedra can be distinguished from white piedra (Langeron 1929 1936) by its purely tropical distribution by the color of the nodules (dark brown to black and opaque) by their greater hardness and adherence Mycologically it is distinguished by its causal agent an Ascomycete (*Piedraia hortai*) with asci forming dark and compact colonies White piedra on the other hand is characterized by grayish or light brown less adherent and softer nodules It is produced by *Trichosporum beigelii* (Rabenhorst) Vuillemin 1902

HISTORY

Black piedra was probably discovered in Colombia from observations of Osorio and Posada in material sent to Desenne (1878) but more definite information resulted from studies made by the Brazilian investigators Godinho (1906) Muniz and Valladares (1907) Rabello (1909) and Horta (1911) Later the affection was observed in other countries of the American continent where the disease predominates although it has also been described outside of the New World

GEOGRAPHIC DISTRIBUTION

The disease exists in hot and humid regions with abundant rainfall It is very frequent in Colombia and Brazil and has been described in the Guianas Venezuela Uruguay Paraguay, and Argentina The affection has been described in Borneo Java and French Indo China

EPIDEMIOLOGY

Although there is no racial predisposition to the disease it is observed that natives of both sexes and of various ages are preferentially attacked due to lack of cleanliness The disease is contagious and may result in family or school epidemics

SYMPTOMATOLOGY

The hairs of the scalp alone are attacked They are covered with small nodules of variable size from about ½ or ¼ the diameter of the invaded hair to about twice its diameter Their color is dark chestnut brown to black The entire circumference of the hair is rarely involved The nodules occur along the longitudinal axis of the hair and are of greater diameter in one extremity than in the other terminating abruptly at this point while they narrow progressively toward the other extremity They adhere firmly to the hair,

due to the fact that the fungus has penetrated beneath its superficial layer without reaching the cortex, so that the hair retains its resistance. These tiny nodes occur in variable numbers, sometimes scattered and not so numerous, sometimes abundant and confluent, forming on the hair a covering which appears spindle shaped or conical. At times there is a single lateral projection. When the nodules are few and small, they may be found only by touch or microscopically, but when abundant, they appear as dark spots or patches in the hair.



Fig 367.—Large and small nodules of black piedra

ETIOLOGY

The fungus which produces black piedra belongs to a group of the Ascomycetes. Horta (1911) was the first to establish clinical and mycologic differences between black and white piedra. Fonseca and Leao (1928) created the genus Piedraia, to separate the causal agent of black piedra from Trichosporum, in which is included the species that causes white piedra and to which the genus Piedraia is not related. Langeron (1929) showed that Piedraia is an Ascomycete of the class Pyrenomycetes, related to the biologic group of the Asterineae of Arnaud (1918), the last being a group of Ascomycetes with a different systematic position. They are adapted to superficial parasitism on leaves of plants. Since they are entirely superficial they require great atmospheric humidity in order to exist. Piedraiae, parasites of human hair, is the equivalent of Arnaud's Asterineae, parasites of plant leaves. Its geographic distribution follows precisely the regions of "asterineic climate," a term which designates very hot and humid climates in which these fungi exist.

There are 2 species: *Piedraia hortai* (Brumpt) Fonseca and Leão, 1928, and *P. venezuelensis*, Brumpt and Langeron, 1934. The validity of the species *P. javanica* Boedyn and Verbunt, 1938, is doubtful.*

P. hortai.—This is the only species which has been cultivated, inasmuch as *P. venezuelensis* was differentiated only by morphologic differences observed in the hair. *P. hortai* in the hair forms parallel filaments, perpendicular to the surface of the hair. The

*Editor's note (O. F.). This opinion is not shared by all authorities.

hyphae are composed of chains of globular or quadrangular cells closely united by means of an interstitial substance, and constitute a dense stroma

Among the filaments asci are found The stroma is therefore fertile, or an ascostroma The asci contain 2 to 8 ascospores These are fusiform, with polar filaments *P venezuelensis* differs by having asci with only 4 ascospores, thicker walls and a strong short, pointed end of the ascospores which takes the place of the polar filament

Colonies of *P hortai* are hard, adherent heaped, dark almost black, with a chestnut colored pigment which diffuses into the medium Between the hyphae, asci with ascospores like those seen on the hair may develop

P sarmentoi Pereira Filho, 1930, and *P paraguayensis* (Delamare and Gatti, 1928) are synonyms of *P hortai*



Fig 368 — Ascospores of *Piedraia hortai* in a section of culture

LABORATORY DIAGNOSIS

A hair containing a nodule is placed in 20 per cent potassium hydroxide between slides, and after heating until bubbles appear is examined under the microscope using medium high power lens Closely septate hyphae with round and quadrangular cells perpendicular to the hair axis with asci containing 8 ascospores and a polar filament or 4 ascospores without filament, are seen The first is *P hortai* the second *P venezuelensis*

To culture *P hortai* the parasitized hair is placed on Sabouraud's 2 per cent dextrose agar Colonies develop slowly with the characteristics described above

TREATMENT

Shave the hair and after thorough cleansing apply daily 5 per cent salicylic acid solution in alcohol petroleum ether or mercury bichloride 1 1000 until the hair becomes normal

MYCOSIS TROPICALIS DUE TO DERMATOPHYTES

The term dermatophytosis applies to diseases caused by a group of fungi that are well defined from the standpoint of mycology physiology, and pathology They have the common characteristic of attacking only structures of superficial keratinized areas Invasion of subcutaneous tissues is very exceptional Mycosis produced by these fungi is known as dermatomycosis

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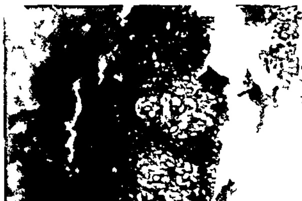


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Classification of this group, which until recently was rather confused, has been tending toward simplification, due to the studies of Ota and Langeron (1923), Taniguchi (1927), Langeron and Milochevitch (1930), Emmons (1934), Conant (1944), and many others, so that at the present time the species considered valid have been grouped by Emmons (1934) into 3 genera, this is the accepted classification

The real situation in the complicated problem of dermatophytes is given in Table XXIV Tropical species of dermatophytes which have not been studied by the authors and which are doubtful are not included In the Crateriforme group we have reduced *Trichophyton epilans, sabouraudi,* and *sulphureum* to *T tonsurans** (Gonzalez Ochoa and Romo Vazquez 1945)

TABLE XXIV

(From Conant et al, 1944)

TRICHOPHYTON Malmsten, 1845 (hair skin nails)	*MICROSPORUM* Gruby, 1843 (hair skin)
A Group Gypseum 1 *T mentagrophytes*	1 *M audouini* 2 *M canis* 3 *M gypseum*
B Group Rubrum 2 *T rubrum*	
C Group Crateriforme 3 *T tonsurans*	*EPIDERMOPHYTON* Lang 1879 Ota and Langeron emend, 1930 (skin nails)
D Group Faviforme 4 *T schoenleini* 5 *T concentricum* 6 *T ferrugineum* 7 *T violaceum*	1 *E floccosum*
E Group Rosaceum 8 *T megnini*	

In keeping with the practical nature of this section, we shall give mycologic data of the 3 genera comprising the dermatophytes with a description of each species as the respective diseases are considered For a study of the other species of dermatophytes the reader is referred to Conant et al (1944)

LABORATORY DIAGNOSIS OF DERMATOPHYTOSIS

Diagnosis is made by direct microscopic examination of the pathologic material and by culture The first procedure is simple and is based on the knowledge of the morphology, filaments in scales and nails and arthrospores in hair Cultivation of the dermatophyte requires knowledge of mycology, especially of contaminants

Filaments—Fragments of parasitized scales or nails are placed between slides in a drop of Amann s chlorolactophenol or 20 per cent potassium hydroxide and examined

*Conant in Dubos Bacterial and Mycotic Infections of Man J B Lippincott Co 1948 pp 590 594 lists in the Crateriforme group only *T tonsurans* but added *T discoides* to the pathogens

microscopically Filaments are observed, the number varying according to the intensity of the process and the causative organism These filaments are ramified, septate They are formed by long articulations, similar to bamboo stalks, or by cuboid cells arranged in chain formation It is important not to confuse these with the "mosaic fungus," an artefact resulting from preparation, the significance of which is very much discussed This formation simulates filaments, but the principal differential characteristic is that it follows the outlines of cells, while true mycelial elements cross through the cells

There is no distinctive characteristic in the morphology of the filaments when they are observed in lesions The different species and genera have filaments that are rather similar In order to determine the species or the genus to which it belongs, it is necessary to cultivate the pathologic material

Arthrospores—Arthrospores are observed by following the same procedure as for filaments They are spherical cells of different sizes, arranged in various forms within *(endothrix)* or outside *(ectothrix)* the hair, dependent upon whether they are of the genus Trichophyton or Microsporum The ectothrix type can be *megasporic* when the spores are larger than 6 microns, and *microides* when the arthrospores are small, 2 or 3 microns In favus, a special type of ectothrix, the arthrospores are medium sized and there are filaments and air bubbles within the hair

In the genus Microsporum, the spores are small, 2 to 3 microns, arranged outside the hair, forming a sheath so that they resemble the microid type of Trichophyton While Trichophyton occurs in parallel lines Microsporum spores are grouped in a mosaic formation

Epidermophyton does not attack hair

Collection of the Material

When scaly lesions of the hairless skin are to be examined, the scales should be taken from the active part of the lesion which is generally the periphery When there are vesicles, the tip of the vesicle should be cut off with scissors With nails, it must be determined first whether the selected section is morbid, by observing any modifications which are present It is necessary to examine several preparations

When hair is infected, the short broken hair or the grayish, opaque hair which appears abnormal to the naked eye should be examined The reliability of diagnosis depends upon the selection of material

Culture

Selected material is cultivated on 2 per cent dextrose agar Seeding may be made immediately, or the selected material may be kept for 1 week, thereby minimizing the possibility of bacterial contamination Culture is made at laboratory temperature After 3 weeks, microscopic and macroscopic examinations are made

MICROSCOPIC ELEMENTS OF THE DERMATOPHYTES

A portion of culture is placed in a drop of Lugol solution, carefully teased, and observed microscopically Two types of elements are observed vegetative and reproductive

Vegetative Forms

(1) **Mycelium**—Septate filaments, without any special characteristics

(2) **Pectinate Bodies**—Filaments enlarged at the extremity with lateral prolongations resembling a comb

(3) **Racquet Mycelium**—Enlargement of one extremity of a segment of the mycelium

(4) **Nodular Bodies**—Rounded masses composed of interlacing mycelium

(5) **Favic "Chandeliers"**—Thickened and ramified filaments resulting in a reindeer antler like formation

(6) **Coiled Hyphae Spirals**—Filaments in coils

LITTLE KNOWN TROPICAL DERMATOMYCOSES

Under this title are included 2 types of dermatomycoses generally considered as trichophytic, although this is probably not true from the appearance which the parasite assumes in the scales They have in common the clinical aspect and the morphology of the causal agent found in the lesions as well as the little that is known of the mycology of these diseases One is the "tinea tropica of Sabouraud the other is the "tinea nigro circinata" of Castellani

Tinea Tropica of Sabouraud

Tinea tropica of Sabouraud is a chronic circinate dermatosis observed in patients from Indo China and Japan It shows erythematous spots rounded and covered with thin scales which as they develop form scaly circinate contours the center of which darkens until it is a blackish color Uncovered parts of the body are affected It is found most frequently in the lower half of the body

Tinea Nigro Circinata of Castellani

This dermatosis has been described as being formed of blackish salient rings sometimes crust like leaving the skin very dark and without alteration It would be similar to tinea tropica' of Sabouraud but might differ from it in that the latter might be more readily curable

ETIOLOGIC AGENT

In the scales of both of these tineas there may be seen mycelial elements short 3 to 4 microns in diameter banana shaped and round spores

The parasite has not been cultivated but Castellani has given the name *Trichophyton blanchardi* to the agent of Sabouraud's tinea tropica and *T ceylonense* to tinea nigro circinata

If the morphology of the parasite in the scales is considered together with the fact that it has not been cultivated to date it may be supposed that this is not in reality a dermatophyte but rather *Malassezia furfur*, the agent of pityriasis versicolor or some similar fungus

TREATMENT

Application of iodine or of chrysophanic acid should be sufficient

PITYRIASIS VERSICOLOR

Synonyms—Tinea versicolor, liver spots tinea flava hodi potsy, tinea furfuracea

DEFINITION

Pityriasis versicolor is a superficial affection of the skin caused by *Malassezia furfur* It is characterized by yellowish brown hypochromic lenticular spots, with thin scales

GEOGRAPHIC DISTRIBUTION

This superficial mycosis is observed throughout the world but it is seen especially in tropical zones where profuse sweating favors its development The var ous modifications in appearance color and s te of the spots found in various tropical regions have resulted in the fact that the d sease has l een described as several different clin cal entities

SYMPTOMATOLOGY

The spots of pityriasis versicolor ha e been descril ed in many different localizations in the patient, but the efflorescences generally occur on the trunk less often on the lower part of the abdomen the shoulders occasionally on the neck, head arms and legs The color varies in different geographic regions among patients in the same region and even in the same patient during the course of the disease The color is usually yellowish or dark brown at times with a slightly erythematous base The spots are slightly scaly pulverulent or smooth with a greasy appearance A diagnostic peculiarity is that the horny epidermis is less adherent than is normal and upon scratching is de tached in small flakes With the exception of slight pruritus in some cases there are no subjective manifestations

It attacks the young rather than older subjects and is seen more often in men than in women It begins with small punctiform macules which tend to grow and by confluence become large spots with irregular outline Ordinarily they measure from ⅙ to 1 cm

In tropical zones the disease is highly contagious The period of incul a tion seems to be one month Duration is long indefinite with but little tendency to spontaneous cure

CLINICAL FORM

Several clinical forms have been described varying according to localiza tion extension size color and shape of the lesions We shall particularly refer to *pityriasis versicolor of tropical regions* and to *pityriasis versicolor alba*

Included in the first type are *pityriasis versicolor flava* of Castellani fre quently found in southern India Ceylon Malaya Java China and Indo China it shows spots of dark yellow or orange color localizing on the face neck chest and abdomen The *parasitic achromia of Jeanselme* or *hodi potsy* observed in the Indies Ceylon Indo China Nigeria Madagascar and Brazil is charac terized by hypochromic spots of irregular outline which localize on the face they are thin scaled and present a definite seasonal recrudescence In the scales of this dermatosis are found elements identical with those of classical pityriasis versicolor Although Fontoynont and Carougeau isolated a Hormo dendrum the etiology is unknown

Pityriasis versicolor alba is not limited to tropical countries It has numer ous synonyms It is similar to typical pityriasis versicolor in the shape, des quamation and size of the spots but is characterized by achromic spots It varies at times in its localization since it is frequently observed on the neck

and arms In making a differential diagnosis of this achromic variety it is important to keep in mind mal del pinto and leprosy

Numerous theories have been advanced to explain the pathogenesis of this clinical form Two of these have been supported by facts One of these theories is that the parasite acts as a curtain to stop the solar rays so that only the normal skin around the spots is pigmented The second theory explains the decolorization of the spots by attributing it to the action of the parasite since spots may be localized in areas not exposed to the sun Depigmentation may be due to metabolic products of the fungus which by histologic modifications may cause a decrease or absence of pigment This white variety is very common in the Pacific coast regions of Mexico

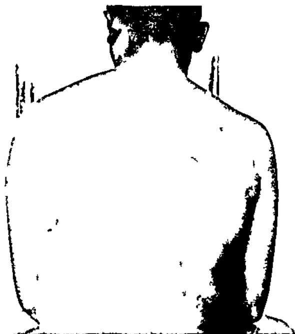


Fig. 472.—Pityriasis versicolor White variety The large hypochromic zones are similar in appearance to mal del pinto

ETIOLOGY

The etiologic agent of this parasitosis is *Malassezia furfur* (Robin) Baillon 1889 There are numerous synonyms of which *Microsporum furfur* Robin 1853 is the most commonly used

Numerous attempts to cultivate the organism have been made but to date the results obtained by those who claim to have been successful have not been duplicated

LABORATORY DIAGNOSIS

Observation of the parasite is easy because of its abundance in the scales Place the scales between slides in a drop of chlorolactophenol or in 10 per cent potassium hydroxide in order to observe clusters of spores and numerous short filaments The filaments are

irregular septate or continuous often flexed angular or straight from 2 to 3 microns in diameter The spores are spherical or ovoid some with thick wall others showing gemmation the diameters vary from 3 to 8 microns They are grouped in masses of 10 to 30 elements

TREATMENT

Desquamation with salicylated petroleum jelly or alcohol is recommended before application of parasiticides Useful parasiticides are 10 per cent sodium thiosulfate (sodium hyposulfite) tincture of iodine diluted 1 3 and 2 per cent chrysarobin It is necessary to continue treatment for several weeks after apparent cure to prevent recurrences Disinfection of clothing is necessary

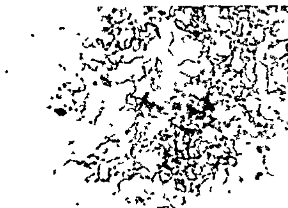


Fig 373 —Parasitized scale of *Microsporum furfur* Note especially the short, flexuous filaments

TINEA NIGRA AND KERATOMYCOSIS NIGRICANS PALMARIS

Tinea nigra and keratomycosis nigricans palmaris are 2 parasitic affections of the skin characterized by black spots Some authors such as Silva (1929) Almeida (1939) and Area Leão et al (1945) believe that this is only 1 affection but that it localizes differently according to the geographic region in which it is found These forms are not well known either clinically or mycologically They might be caused by 1 or 2 species belonging to the genus Cladosporium

Tinea Nigra

Tinea nigra was discovered in south China by Sir Patrick Manson in 1872 It was found by Castellani in Ceylon (1905) It has also been observed in India Java and the Malay States

It is seen in the form of black spots not pruriginous spreading slowly and slightly scaly It is localized on the trunk and the neck although it may be found in any area of the skin with the exception of the face

Keratomycosis Nigricans Palmaris

Keratomycosis nigricans palmaris was observed by *Cerqueira in Brazil* in 1891 It was later studied by several Brazilian authors This condition has been reported in Cuba (Pardo Castello 1938) and in Panama (Welsh 1948)

It is characterized by the appearance of black spots made up of small black dots They are of various dimensions, with little or no pruritus, and are localized on the palms of the hands

Neves and Costa (1947) agree with Almeida (1939) and Silva (1929) in considering the 2 conditions as 1 and propose the name "tinea nigra" for both of them, recommending the use of the word *palmaris* to indicate the palmar localization frequently found in Brazil



Fig 374 — A case of tinea nigra, characterized by numerous black points in the palmar arch (Photograph by Area Leão et al Rev Brasil Biol., 5)

ETIOLOGY

Two species are considered *Cladosporium mansoni* Castellani, 1905, for tinea nigra and *C werneckii* Parreiras Horta 1921, for the Brazilian type

LABORATORY DIAGNOSIS

The appearance of the parasite is the same in both forms The scales or, when the lesion is not scaly slivers of skin obtained by slicing the surface layer with a razor blade are found parasitized by straight or flexed filaments composed of short cells, dark colored, with thick walls In addition to these, there are other elements, rounded, uniseptate or pluriseptate Culture is readily obtained by seeding in the usual media (Sabouraud 2 per cent dextrose agar) Colonies are blackish, moist at the beginning, later downy They are formed by fuliginous filaments which break into spherical arthrospores, and colored hyphae terminated by elliptical conidia provided with disjunctors



Fig 375 —Scale of *tinea nigra*, showing filaments of *Cladosporium wernecki* (Photograph by Area Leão et al Rev Brasil Biol 5)



Fig 376 —Culture of *Cladosporium wernecki* *A* in carrot *B*, in potato *C*, in Sabouraud's glucose solution

TREATMENT

Drugs used in the treatment include keratolytics such as 3 per cent salicylic acid in alcoholic solution and fungicides such as 3 per cent resorcin ointment or tincture of iodine

TINEA ALBIGENA

DEFINITION

Tinea albigena, also called *Thi kuen*, its native name, is a chronic condition localized in the soles of the feet and the palms of the hands It is characterized by *keratosis and eventually by definite residual depigmentation*

Langeron (1936) states that Nieuwenhuis described the disease in 1904



Fig 377 —Microscopic morphology of *Cladosporium wernecki* *A*, septate filaments showing conidia between them *B* conidia provided with disjunctors some show buds

GEOGRAPHIC DISTRIBUTION

It is found in about the same areas as those in which tokelau is endemic, that is, in the islands of the Pacific, Indo China, Malay Archipelago, and Ceylon It appears that the dermatosis described in the Cameroons as *partial albinism* and the disease called *calor de figo* in Brazil both correspond to tinea albigena

SYMPTOMATOLOGY

There are 3 stages of development The *initial, vesicular* stage is marked by appearance of large, pruriginous vesicles which, upon breaking, leave the Malpighian layer uncovered This exposed surface becomes keratinized and thickens, and the disease passes to the second stage, the stage of *keratosis,* also called *chronic* The affected areas continue to thicken, fissures are produced,

and the pruritus diminishes but the thickened zones become more painful. This may persist for the remainder of the patient's life and in some cases invasion deeply into the tissue may cause destruction of pigment—the third stage or *depigmentation*. Hyperkeratosis is more intense in the feet than in the hands. From this localization the process may extend to the dorsum of the hand or foot as well as to the forearm and leg.

Spontaneous cure occurs very rarely and after many years.

The nails are attacked and they become thick and brittle.

DIFFERENTIAL DIAGNOSIS

In making a differential diagnosis mal del pinto, palmoplantar keratosis, leprosy and syphilis should all be considered.

ETIOLOGY

The scales show filaments similar to those of a dermatophyte but with a characteristic double contour and oval spores, these being abundant in nails. The chlamydospores are found along the length of the filaments.

Culture was obtained by Nieuwenhuis (1908) who was the first to observe the parasite in the scales; he classified it as *Trichophyton albiciscans*. Later Ota (1925) demonstrated that it is not a Trichophyton but a Glenospora.

Glenospora albiciscans (Nieuwenhuis 1908) Ota 1925 grows slowly, producing colonies with a downy coremioid surface, light brown in color. Filaments 2 to 3 microns in diameter, with thick walls and double contour, are observed under the microscope. The reproductive apparatus is formed of sessile spores along the length of the filaments or at their ends. These are oval, 7 by 3 microns, and brown.

LABORATORY DIAGNOSIS

Laboratory diagnosis is made by examining scales between slides in a drop of potassium hydroxide solution or in Amann's chlorolactophenol. The scales show filaments, spores and chlamydospores. Culture is obtained by seeding parasitized scales in Sabouraud's 2 per cent dextrose medium.

TREATMENT

The same treatment is used as that employed in other dermatomycoses but in greater concentration. Keratolytics such as 6 per cent salicylic acid and fungicides such as tincture of iodine and chrysarobin 10 per cent are indicated. Ten per cent chrysarobin is especially recommended by Nieuwenhuis (1908).

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CHAPTER 50

DEEP TROPICAL MYCOSES

ANTONIO GONZALEZ OCHOA

Deep mycoses are diseases produced by fungi which in addition to invading the skin or mucosa also invade other structures such as muscle, bone, viscera, etc This type of mycosis is also called *systemic* or *generalized mycosis*

Only deep mycoses of major incidence in the tropics will be discussed in this chapter For information regarding cosmopolitan mycoses, the reader is referred to standard works on the subject We shall discuss maduromycotic mycetoma and actinomycotic mycetoma due to aerobic actinomycetes, chromoblastomycosis South American blastomycosis,* and rhinosporidiosis

MYCETOMAS

Mycetomas are deep mycoses found in many areas There is confusion regarding the extent and significance of the term "mycetoma" in the clinical subdivisions and in the synonyms by which it is designated We shall attempt to clarify and explain existing up to date facts

DEFINITION

Mycetomas are chronic, granulomatous infections, characterized by the formation of multiple abscesses and sinuses The exudate from the lesions contains aggregations of mycelia with a characteristic granular form

HISTORY

It appears that this disease has been known since ancient times Under the name *Padaualmicum* descriptions are found, in India, of a disease of the foot, with tiny tumors, which after a year or longer, suppurate and discharge a peculiar fluid The difference between this affection and *slipatham* or elephant foot, was also established in ancient times, and mycetoma was probably thus differentiated from elephantiasis

In 1712 Kampfer, in India, referred to a tumor of the foot called *pericai* which may have corresponded to mycetoma, elephantiasis, or frambesia Two years later Pondicherry (1714) referred to a tumor of the foot which, from his description, was probably mycetoma These early references were followed by those of Heyne (1806), Brett (1840), and others but these added no further information

During Gill's administration of the Madura Dispensary (1842), a tumor and fistulous disease of the foot was known to physicians Gill wrote a clear description of this disease and reported that a peculiar ailment existed in the region, characterized by marked deformity of the foot and by fungous excrescences from which oozed a watery liquid He insisted that this particular disease differed morphologically from any other known clinical entity His successor at the dispensary, Colebrook (1846), confirmed Gill's observations and called attention to the fact that the condition was known as "Madura foot" in various regions of India This name was adopted and is still in use at the present time

*Chapter 51

Rustomj n 1808 pre ente l a cl n al descr pt on of Madura foot l ... cases A short t me later (1860) Eyre referred to the granules and ... t ssue in Ma lura foot contained small tubercles resembl ng fish eggs

Carter cont nu ng the work of Eyre and follo ing the cl n al les r p ... made a ser es of stu l es wh ch ere publ led in 18 4 under the t tle On ... *Fungus D sease of Ind a* Th s s st ll the class c treat se on th s ... been impro ed upon to date He expla ns that the cau al organ n s a ... 2 k nds of granules appear in the pus—one black sh called *melano d* the ... called *ochro d*

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The first lefin te des r p ... of a t n o ... d s o ere l accumulat ons of n ... he ello ... gra ul s onta e l n max llary ... e co ... publ ... ed by Boll nger n

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Once prec e kno ledge perta n ng to act on ... had been obta ned all mycet ... cases were nclu led un ler that ent ty that s a t non yco ... Due to the fact that the ... of Boyce and Surve or con ern ng the var et es of mycet ma were lefin tely proved w ... Vincent in North Afr ca 18 4 su ceeded n cult vat ng Act nomyces from the ochr ... var ety of mycetoma le called ... *Str ptoth x madu ae*) and Wr ght (1898) in No ... Amer a obta ned a ... fro a ulture f the melano l granules the confus on pers s ... unt l Chalm rs and Ar h ball in a ser es of stu l es (1916 to 1918) rev ... a t non yco ... my etoma and Ma lura foot and ... al

guinolent substance is discharged from the small orifices which alternately are occluded and reopen The tissue surrounding the initial lesion begins to show reaction while other initial lesions, similar to the first, appear in the vicinity at variable intervals, from 1 to 6 months, resulting finally in swelling and deformation, due to fibrous tissue reaction and sinus formation

When the disease has become established, a great increase is observed in the volume of the diseased area in which numerous nodules are seen Each of these nodules corresponds to the external orifice of a fistula proceeding to the deeper parts A thin shiny rosy cutaneous lamina covers the opening and, when it is lifted a rosy "eye" of somewhat "gelatinous" tissue is observed crowning the vertex, through the tiny orifices of which exudes a fluid containing the characteristic granules The exudate is generally threadlike,



Fig 378 —Actinomycotic mycetoma characterized by great increase in size of diseased zone which is covered by fistulous orifices

yellowish, sometimes sanguinolent, and when associated infection is present, it is decidedly purulent and of a bad odor The granules, in most cases, are yellowish white varying in size and number from few to many, resembling caviar In some cases, necrosis of the small nodules results in formation of ulcerations of various sizes and shapes, according to individual cases The ulcers develop slowly

The fistulae tend to close temporarily, by a crust or even scar formation New fistulae constantly form, while others are closing and sometimes disappearing Formation of a fistula is preceded by the appearance of a small nodule which later opens The small nodules appear in varying numbers and, although they are very frequent, they may be absent in some cases, the fistula

opening at the base of the skin They vary considerably in size being 2 to 6 mm in diameter by 3 to 5 mm in height They may be isolated or confluent The color varies from the color of the skin to red and violet The fistular orifices



Fig 3"9 —Podal mycetoma by *Nocardia* [illegible] showing a large number of nodular elements



[illegible]350 —Case of actin[illegible]mycetoma in which nodular formations are lodged in a [illegible]pression giving an umbilical appearance (corresponds to suppurative type of Louffard)

[illegible]he crown of the nodule vary in size and number Sometimes they are pres[illegible] in craterlike depressions or more rarely there is a depression and a slight [illegible]minence in this depression contains the fistular opening which looks some[illegible]t like an umbilicus

The fistulae penetrate deeply into the tissues of the affected region old cases or in cases where the infection is heavy they may penetrate into bone and cause cavernous expansion at the deep end of the path of invas Until recently it was thought that there were certain species of fungi wl cause mycetomas which attack the bone while other species do not It appears that penetration of bone tissue does not depend upon any defi species but rather on the stage of development and on the intensity of the fection since in all old cases invasion of bone tissues is constantly obser When the joint is invaded the subsequent destruction of ligaments and art lar surfaces results in ankylosis Muscles appear to be particularly vul able It may be stated that in general no tissue is respected by the f which cause mycetoma

Invasion occurs through contiguity and when there are distant les they seem to be caused by autoinoculation rather than through blooc lymphatic metastases There are cases in which gland and even visc metastases occur but this is exceptional reports concerning this still r verification On the other hand visceral invasion by contiguity is not r especially in thoracic mycetoma in which there is almost always a pulmor attack

Macroscopic Changes—It is easy to observe that regions attacked mycetoma show alterations consisting of increase of subcutaneous cell tissue and almost complete disappearance of muscle and adipose tissue repla by connective tissue

Within the diseased tissue bones muscles etc there are numerous sini tracts which terminate at the inner end in cavernous expansions In the cei of these channels are found gelatinous or necrotic material containing granu these are also observed within the diseased tissue The bones are softened carious and numerous fistulous tracts are found Articular surfaces are roded with tendon destruction

Microscopic Changes—Microscopic changes are the same for all cai agents of mycetoma We shall follow fundamentally the observations Boyd and Crutchfield (1926) They reported that in the true skin the M pighian layer becomes thinner with the germinal stratum projected inw Atrophy of the papillae and marked hyperplasia of connective tissue imm ately below the epidermis are observed between the germinal stratum glands There is a leucocytic infiltration composed more frequently lymphocytes than of polymorphonuclears The glands are atrophied or rounded by a fibroblastic proliferation In almost all cases there is an crease in vascularization and hemorrhage in the corium

In a section of a nodule the Malpighian stratum is even more slen and the papillae are markedly atrophied When the small nodule is accompar by fistulae the horny layer is destroyed and the tissue surrounding the noc presents considerable hyperplasia of the reticular and also of the papill zones The nodule is filled with an accumulation of polymorphonuclears lymphocytes among which numerous granules may be observed When

nodule has not yet fistulized it presents hyperplasia of young connecti tissue with considerable infiltration of mononuclear cells and numerou capillary vaults. The nodules may be formed as a result of an internal pres sure due to cellular infiltration.

In deep seated tissues there is a characteristic extensive hyperplasia of connective tissue which parallels extension of the disease with hyaline degen eration after the process recedes. Adipose tissue is replaced by connective tissue and the remaining areas are infiltrated with lymphocytes. While the invasion of connective tissue is recent an increase of vascularization is ob served, this disappears with the degeneration of connective tissue. San guineous extravasation is almost constant with observation of red cells or blood pigment. There is perivascular infiltration with mononuclear cells.

The fistulae may have a definite wall or they simply open into the con nective tissue their internal portion is infiltrated with mononuclear cells and when granules are here observed they appear to be surrounded by poly morphonuclears or epithelioid cells. Sometimes giant cells are seen near the granules. In some areas the disposition of the epithelioid cells and of the lymphocytes resembles a tubercle.

Frequently Russell bodies are seen isolated or grouped and of various sizes.

Diagnosis is established only by finding the granules since there is no specific tissue reaction because the histologic modifications may be due to a purulent infection with polymorphonuclears or to chronic inflammation with granulation tissue and dense invasion of connective tissue (Fig 396).

In sections stained with hematoxylin eosin the central portion of the granule takes the hematoxylin stain while the periphery or the clubs stain better with eosin. To be able to observe the structure of the center of the granule it is best to stain the section by the Gram method. The slender fila ments of the actinomycotic granule can then be seen quite different from the thick filaments and chlamydospores of the maduromycotic granule. Both ypes of fungi being gram positive stain intensely and are easily differenti ated. This method of staining is also convenient when the granules are pro uced by bacteria since they can be clearly seen.

Clinical Picture

The frequency and clinical picture of mycetoma vary according to its alization. Localization may be divided as follows: mycetoma of the ex mities mycetoma of the thorax mycetoma of the abdominal wall and other alization.

We should like to repeat that we are not concerned in this chapter with tions due to *Actinomyces bovis* but only with those due to aerobic actino tes (Nocardia) and the fungi of maduromycotic mycetoma.

Mycetoma of the Extremities.—The most frequent localization of my a is in the extremities especially the foot and for this reason most synonyms for the disease imply morbidity of the foot such as adipose

The fistulae penetrate deeply into the tissues of the affected region In old cases or in cases where the infection is heavy they may penetrate into the bone and cause cavernous expansion at the deep end of the path of invasion Until recently it was thought that there were certain species of fungi which cause mycetomas which attack the bone while other species do not It now appears that penetration of bone tissue does not depend upon any definite species but rather on the stage of development and on the intensity of the infection since in all old cases invasion of bone tissues is constantly observed When the joint is invaded the subsequent destruction of ligaments and articular surfaces results in ankylosis Muscles appear to be particularly vulnerable It may be stated that in general no tissue is respected by the fungi which cause mycetoma

Invasion occurs through contiguity and when there are distant lesions they seem to be caused by autoinoculation rather than through blood or *lymphatic metastases There are cases in which gland and even visceral* metastases occur but this is exceptional reports concerning this still need verification On the other hand visceral invasion by contiguity is not rare especially in thoracic mycetoma in which there is almost always a pulmonary attack

Macroscopic Changes—It is easy to observe that regions attacked by mycetoma show alterations consisting of increase of subcutaneous cellular tissue and almost complete disappearance of muscle and adipose tissue replaced by connective tissue

Within the diseased tissue bones muscles etc there are numerous sinuous tracts which terminate at the inner end in cavernous expansions In the center of these channels are found gelatinous or necrotic material containing granules these are also observed within the diseased tissue The bones are softened are carious and numerous fistulous tracts are found Articular surfaces are corroded with tendon destruction

Microscopic Changes—Microscopic changes are the same for all causal agents of mycetoma We shall follow fundamentally the observations of Boyd and Crutchfield (1926) They reported that in the true skin the Malpighian layer becomes thinner with the germinal stratum projected inward Atrophy of the papillae and marked hyperplasia of connective tissue immediately below the epidermis are observed between the germinal stratum and glands There is a leucocytic infiltration composed more frequently of lymphocytes than of polymorphonuclears The glands are atrophied or surrounded by a fibroblastic proliferation In almost all cases there is an increase in vascularization and hemorrhage in the corium

In a section of a nodule the Malpighian stratum is even more slender and the papillae are markedly atrophied When the small nodule is accompanied by fistulae the horny layer is destroyed and the tissue surrounding the nodule presents considerable hyperplasia of the reticular and also of the papillary zones The nodule is filled with an accumulation of polymorphonuclears and lymphocytes among which numerous granules may be observed When the

nodule has not yet fistulized it presents hyperplasia of young conne[ctive] tissue with considerable infiltration of mononuclear cells and nume[rous] capillary vaults The nodules may be formed as a result of an internal p[res]sure due to cellular infiltration

In deep seated tissues there is a characteristic extensive hyperplasia [of] connective tissue which parallels extension of the disease with hyaline deg[en]eration after the process recedes Adipose tissue is replaced by connecti[ve] tissue and the remaining areas are infiltrated with lymphocytes While t[he] invasion of connective tissue is recent an increase of vascularization is o[b]served, this disappears with the degeneration of connective tissue San[guineous] extravasation is almost constant with observation of red cells o[r] blood pigment There is perivascular infiltration with mononuclear cells

The fistulae may have a definite wall or they simply open into the connective tissue their internal portion is infiltrated with mononuclear cells and when granules are here observed they appear to be surrounded by polymorphonuclears or epithelioid cells Sometimes giant cells are seen near the granules In some areas the disposition of the epithelioid cells and of the lymphocytes resembles a tubercle

Frequently Russell bodies are seen isolated or grouped and of various sizes

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Clinical Picture

The frequency and clinical picture of mycetoma vary according to its localization Localization may be divided as follows mycetoma of the extremities mycetoma of the thorax mycetoma of the abdominal wall and other localization

We should like to repeat that we are not concerned in this chapter with infections due to *Actinomyces bovis* but only with those due to aerobic actinomycetes (Nocardia) and the fungi of maduromycotic mycetoma

1 **Mycetoma of the Extremities** —The most frequent localization of mycetoma is in the extremities especially the foot and for this reason most of the synonyms for the disease imply morbidity of the foot such as adipos

sarcoma of the foot morbus tuberculosis pedis, Madura foot endemic degeneration of the bones of the foot Indian pedal mycosis, caries of the bones of the foot etc

Rural laborers are exposed most frequently to trauma from pricking or scratching by thorns which harbor the causal organisms of mycetoma Since rural people are accustomed to going barefooted it is not surprising that mycosis of the feet or legs is the most frequent form of this condition

Almeida (1939) states that the disease is localized in the lower limbs in more than 60 per cent of the cases of mycetoma observed in Brazil In Mexico an equal number or perhaps a greater percentage of mycetomas occurs in the lower limbs

The length of time which elapses after the injury until the nodules appear varies considerably In some cases even after the wound has completely healed the little painless nodule appears this later develops into abscesses and fistulae and is surrounded by a hard edema with the characteristics described above It may be weeks or even months after its appearance that an other one appears and others make their appearance successively Later, the zones of sclerous tissue which surround the nodules become fused and progressively form a tumor which ultimately destroys the outline of the foot transforming it in advanced cases into a roundish mass in which the toes are mere appendages The mass is covered by small nodules in various stages of development some just forming others undergoing fistulization and exuding the characteristic secretion and granules still others closed or even cicatrized The general consistency of the affected or enlarged foot is very hard although it may have some small fluctuating areas

The deformed foot becomes sensitive although spontaneous pain is rare The leg becomes thin with atrophied muscles and the patient cannot walk more because of the size of the foot than because of the pain The general health of the patient is not much modified when there are general symptoms they are due to associated bacterial infection

Bouffard (1919) in his monograph on mycetoma divided it into *suppurative sclerous,* and *cystic* The most frequently observed type is the *suppurative* which corresponds to the description given here and it is the type most frequently seen in the foot

The *sclerous* form of mycetoma is observed in some cases with pedal localization According to Bouffard it is due to absence of secondary infection so that the fungus itself is alone responsible for the changes The diseased foot is more or less lumpy, very hard covered with tightly stretched skin without nodules and with very few fistulae opening in the skin This type of tumor which in many cases may remain closed slowly tends to total destruction of tissue muscle tendon and bone without suppuration This type appears to be more painful

The *cystic* form of mycetoma consists of a permanently localized tumor without any tendency to spread In this case the area is like a cystic pouch rather delimited containing exudate and granules This clinical form is rarely seen



F g 381 —Act nomycot c myceton of sc erous ty e Tumor la ks n xl l s Sparse fistu ous o fi es are seen n t e t ght skin



F g 38 Myc tot a f t e f t an l l x aft r 8 n onths of e olut on in tial lesion appeared in the foot

Frequently mycetoma of the foot invades the leg early in the disease although on the other hand one often observes lesions of 10 years or longer which remain strictly localized in the foot

After pedal localization in the order of frequency there follows localization in the leg and thigh There is the same characteristic fistulous tumor formation Frequently great hypertrophy of the affected region is observed with fibrous woody consistency in some areas and softness in others The skin is filled with cicatricial spots and cup like depressions with a yellowish crust or containing a fistulous orifice through which oozes a yellowish fluid sometimes containing characteristic granules

Mycetoma of the hands is rare The clinical description of this type as well as mycetoma of the arms and shoulders is the same as above



Fig 383 —Mycetoma of the knee due to *Nocardia mexicana*

2 **Thoracic Mycetoma**—Thoracic mycetoma merits both clinical and etiologic consideration It may originate in the thoracic wall later attacking the pleurae and the lungs or it may be of pulmonary origin and extend to the *thoracic wall* *In the first case the infection works from the outer to* the inner tissue which corresponds to aerobic actinomycetes In the second case the infection is generally caused by the anaerobic actinomycetes *A bovis* We cite the difference only for the purpose of a better understanding of the first (aerobic) situation especially when treatment is referred to Given the habitat ' of the aerobic actinomycetes (plants and soil) it is readily understood that some injury opens a portal of entry to the infecting agent and that due to the invading tendency of mycetoma the lesion after perforating the thoracic wall extends to the pleurae and the lungs The patient frequently reports an injury which gives rise to the formation of an initial nodule which ordinarily appears on the anterior surface of the thorax becoming soft it is fistulized and becomes surrounded by sclerotic tissue With the passage of time similar elements form until the anterior surface of the thorax is trans

formed into a great mass in which zones of woody hardness alternate with soft areas of an irregular surface filled with bumps and depressions umbilical in form covered by scabs of a dirty yellow color and by "eyes" of flesh which extrude a yellowish serous fluid containing the peculiar granules The lumps are formed by subcutaneous adhesions some rather free others adherent and some showing inflammatory reaction in the skin which covers them For many years the disease remains localized in the wall until the patient rather suddenly presents an acute pleural manifestation with purulent discharge followed shortly thereafter by a clearly pulmonary manifestation in which there dominates a physical syndrome of condensation with persistent cough and bloody sputum containing the characteristic granules Prognosis becomes serious when mycetoma invades the lung These cases of visceral repercussion are fatal because they resist every therapeutic measure



Fig 381—Thoracic mycetoma with pulmonary invasion, due to Nocardia mexican

3 **Abdominal Mycetoma**—The statements above are also true fo type The aerobic actinomycetes penetrate from the outside inward a initial lesion appears in the superficial layers of the abdominal wall other hand in infection due to *bovis* the visceral manifestation ofter pendicular picture is the clinical beginning of the case

In the infection due to aerobes a nodule appears in the skin of domen The nodule becomes soft and fistulizes and oily pus containi



Fig 385—Mycetoma of the back.



Fig 386—Mycetoma due to *Nocardia mexicana* in the scapular region



Fig 387—Actinomycotic mycetoma in the axillary region (case of Rico and Medina)



Fig 388—Facial mycetoma due to *Nocardia mexicana*

ules oozes from it The nodule is followed by others until the area shows the characteristic consistency of mycetoma

When the abdominal cavity is invaded the clinical picture depends upon which viscera are affected general symptoms are very severe

4 **Other Localizations of Mycetoma** —Assuming that the agents of actinomycotic or maduromycotic mycetoma may invade any type of tissue it can be understood that mycetoma may appear in any site so that in addition to the most frequent localizations it also appears in the face neck gluteal region etc In all cases the common denominator of mycetoma that which constitutes the clinical picture, is the nodule which softens fistulizes and exudes an oily pus containing granules becomes surrounded by sclerotic tissues and with the appearance of new nodular elements developing by the same process produces a tumor mass with those characteristics discussed under the general clinical picture

On very rare occasions mycetoma acquires a quite different appearance from the usual description It may take the form of a simple hardening of the affected region or it may present ulcerative proliferations similar to epitheliomata

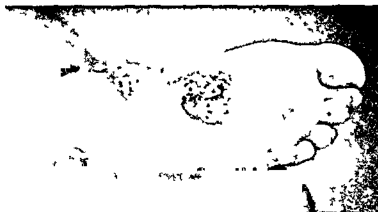


Fig 389 —Ulcerous proliferation similar to neoplasia caused by *Nocardia mexicana*

DIAGNOSIS

Granules

The granules are the pathognomonic elements of mycetoma Diagnosis is not possible without the presence of these granules in the suppurative material or in biopsy tissue The erroneous concept contained in the terms "paramycetoma" and "pseudomycetoma" is evident *Paramycetoma* is defined as a clinical entity in which the granules are absent or are so few and so small that they are not readily observed The term *pseudomycetoma* includes those conditions which simulate mycetoma but are etiologically different such as the tertiary lesions of yaws etc These 2 terms only complicate the picture and lead to confusion

The granules are small formations which have been compared to fish roe They vary in size from tiny specks barely visible to the eye or visible only under the microscope to the size of a pinhead or a little larger These last are composed of aggregations of several small granules They are rounded or lobulated The color is ordinarily yellowish white there are red and black granules but these are very exceptional * In general exaggerated importance is attached to the color of the granules in the study of mycetoma The yellowish white granules are extremely more important than the black and red Apart from the fact that the red and the black granules are rarely found there is no constancy to the fact that the color of granules corresponds to any particular species We have isolated N *pelletieri* from mycetoma with yellowish white granules although this species is regarded as a producer of red granules The fact that different species of fungi produce granules of the same color has already been discussed by Gammel (1927) in treating of maduro mycotic granules He believed that one species may produce different colored granules therefore mycologic classification of mycetoma by the color of the granules is incorrect

The consistency of the granules varies from very soft (so soft that they flatten under a cover glass) to very firm

Because of the importance of the granules in the diagnosis of this type of mycosis it is necessary to observe them in the exudate from the fistulae by removing the crust covering the orifice or by lifting the thin skin cover of the nodule to obtain drops of the oily yellowish fluid which is not as purulent as that of open fistulae

The use of a hand lens aids in discovering them When the granules are too small to be seen with the naked eye the exudate (purulent or nonpurulent) is placed in a drop of Lugol solution or in 10 per cent potassium hydroxide between slides and examined microscopically Sometimes it may be necessary to irrigate the fistulae with saline solution using a syringe in order to introduce the liquid under pressure thus separating the adherent granules from the walls of the fistulae The liquid is then centrifuged The granules will be found in the sediment

Microscopic Examination —The granules are formed by an accumulation of mycelial elements which vary in morphology according to the type of mycetoma In either variety actinomycotic or maduromycotic the granule is generally formed by 2 zones a central zone of filaments and a peripheral zone *formed by hyaline club shaped prolongations which can be compared to* bowling pins and are called clubs '

The central zone of the *actinomycotic granule* is formed of hyphae of an actinomycete The fungus a *microsiphonate* has very slender nonseptate filaments giving the appearance of pressed felt on the surface of which can be seen a structure more punctiform than filamentous Sometimes in Gram stained histologic sections very slender filaments are seen, which have become free from the pressed surface

*Editor's note (O F) This refers only to Mexico



Fig. 390.—Osseous lesions in a case of actinomycotic mycetoma.

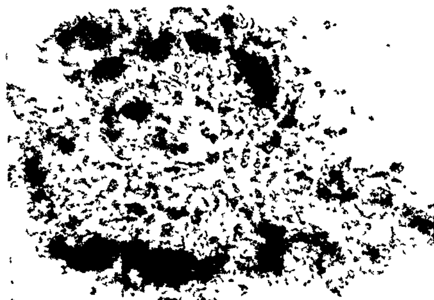


Fig. 391.—Actinomycotic granule stained by the Gram method showing the structure formed by slender filaments of the actinomycete or by a section of these giving the appearance of punctiform elements.

The central zone of a *maduromycotic granule* is formed of fungi belonging to various genera, called *macrosiphonates,* in which the filaments are septate, branching, and wide, in spite of the "pressed" appearance of the accumulation the larger diameter of the component hyphae can be observed In most maduromycotic granules there are numerous chlamydospores

The different appearances described for the central zone as peculiar of some species are of but little significance The fact that a species is described as having a convex or concave contour, or lacunar hollow, or with a characteristic interstitial substance, etc, is of little value in the study of the species, since these are not constant data

The affinity of this central zone for stains depends upon variations conditioned by the biology of the fungi and upon the process of fixation of the biopsy tissue It is known that all the fungi are gram positive and that the "clubs" are acidophilic, being in this respect like the Russell bodies also found in mycetoma When stained by the Gram method, the central zone is blue and the clubs reddish



Fig 392 —Maduromycotic granule due to *Cephalosporium* sp

Clubs —The importance of these elements has been overemphasized In the past, key charts based upon the presence or absence of these clubs were used in the study of the granule producing actinomycetes At the present time it is known that these bodies may be present or absent in the same species, and even in the same patient may be found granules with and without the clubs These elements are not characteristic of fungi which cause mycetoma, being sometimes found also in sporotrichosis tuberculosis, actinobacillosis, and around accumulations of Staphylococcus and even around inorganic substances injected into tissue such as China ink, tellurium, and vanadium salts

Curiously, these formations have been cultivated Wright (1905) obtained a culture of clubs in a liquid medium with organic proteins, Langeron et al (1925) cultivated clubs of *Actinobacillus lignieri* in Sabouraud's 6 per cent dextrose medium, and other authors have succeeded in reproducing these formations Two theories have been advanced to account for the production of these bodies, one theory states that they are products of the parasite itself, the other considers them a reaction of the host to the parasite The latter hypothesis is generally accepted According to Benda (1900), Magrou (1919), Lieske (1921), and others, the formation of these bodies is a phenomenon analogous to the formation of giant cells, not a defensive reaction, but rather a symbiosis

Since these elements are so variable that there are no constant morphologic ... istics for any one species, they are of little value in the study of granules. The ... vary in length, may bifurcate or trifurcate, with or without digitation.

ETIOLOGY

There are various fungi which cause mycetoma, belonging to dif... classes and genera. As stated before, it is not possible to ascertain clini... the fungus causing the disease, since neither the symptomatology nor ... macroscopic appearance of the granules is constant. Culture alone ... clarify the nature of the infecting agent.

The division of mycetomas proposed by Chalmers and Archibald (191... is the most generally accepted and the most logical in that it is based ... etiology. In this classification mycetoma is considered as being caused o... the one hand by various organisms of the actinomycetes group and on th... other hand by fungi belonging to different genera, families, and classes.

Actinomycotic Mycetoma

Actinomycosis Due to Aerobes.—We must repeat that *Actinomyces bovis* is not under consideration and that only the aerobic actinomycetes interest us here from the point of view of tropical pathology.

At the present time, the former genus Actinomyces has been divided into several genera so that the most generally accepted classification, that of Waksman and Henrici (1943), includes the genera Actinomyces, Nocardia, Streptomyces, and Micromonospora. It does not provide for the so-called *Actinomyces madurae* and *A. pelletieri*, so that we shall use the name Nocardia for these 2 species, according to Berger (1948).

The origin of the Actinomycetales and their place among microorganisms has been very much discussed. They have been considered bacteria with very complex biology, degenerated fungi, or a special ancestral group common to bacteria and fungi.

Like other fungi, the Actinomycetales are composed of filaments or hyphae which form the mycelium. The filaments are very slender, branching and nonseptate. Ramification is a distinctive characteristic which is very important in distinguishing them from bacteria, but this is not an absolute criterion since there are a few bacteria like *Mycobacterium tuberculosis* which have ramifications. In some species of Actinomycetales the protoplasm of the filaments collects in granules which later fragment, resulting in the formation of coccoid and bacillary elements. In other genera there is formation of spores.

These fungi present very interesting biochemical characteristics like their capacity to form pigments, so that the colonies are of various colors: orange, red, black, etc. The pigment of some of the species is released and imparts an intense color to the culture medium. The odor of the culture helps to identify the fungi; generally they have an earthy odor.

Their interesting biochemical activity is seen in the enzymatic power of some of the species; this is of fundamental importance in species studies.

Mycetoma Producing Actinomycetales.—The numerous synonyms and the existing confusion within the group of mycetoma producing actinomycetes have complicated the study of these fungi. Not considering *A. bovis*, Gammel (1927), in his study of mycetoma, mentioned 12 species as the cause of this disease. Almeida (1939) considered 11. Lacaz, in his monograph on mycetoma producing actinomycetes (1945), referred to 24 strains of only ... species were used by this author. Without discussing the validity of the species ... different authors or attempting to reduce to synonyms the incorrect species ... ... we shall use the criterion established by those who ...

with this type of mycosis and by our own experience with Mexican cases The species of mycetoma producing Actinomycetales found in the great majority of cases are:

N mexicana (Boyd and Crutchfield, 1921) Ota, 1928
N brasiliensis (Lindenberg, 1909) Castellani and Chalmers, 1913
N madurae (Vicent, 1894) Blanchard, 1898
N pelletieri (Laveran, 1906) Pinoy, 1912
N asteroides (Eppinger, 1891) Blanchard, 1896

Following the classification of Waksman and Henrici (1943), we shall divide the mycetoma producing actinomycetes into 2 groups those which present the phenomenon of fragmentation and those which lack this characteristic The first are partially acid fast, while the second are not, and among the acid fast, some have enzymatic activity and others lack it

To study these characteristics, it is convenient to begin by using a culture made in milk, of a month's development With the fungus cultivated in this medium, a smear is made *with a small portion of the culture, rubbing the material back and forth as much as possible,* on the slide, using a dissecting needle or a Pasteur pipette, until it dries The preparation is then stained by the **method of Umbreit** (1939) for partially acid fast actinomycetes.

Steam in 2 per cent carbol fuchsin for 5 minutes

Wash with running water

Decolorize by immersing the slide in 3 per cent hydrochloric acid for exactly 15 seconds

Wash with water and counterstain with 0 1 per cent aqueous solution of methylene blue for 3 minutes

In cases with fragmentation, a great number of coccoid and bacillary elements and remnants of filaments, red stained, are observed

With the same milk culture, a study is made of the enzymatic activity of the fungus It is necessary only to ascertain whether the fungus liquefies gelatin, since other enzymatic activity parallels the hydrolysis of gelatin The most convenient method is the indirect method (Waksman, 1919) It consists in adding 3 c c of the milk in which the fungus has been cultivated to 10 c c of 15 per cent "Gold Label" gelatin in distilled water After incubating at 37° C for 24 hours, the tubes are placed on ice for 1 hour before reading

To study the colonies, the Actinomycetales are seeded on Sabouraud's 2 per cent dextrose agar and incubated at laboratory temperature and at 37° C for 20 to 30 days

Description of Species

Nocardia mexicana (Boyd and Crutchfield, 1921) Ota, 1928, was isolated for the first time in California from a Mexican subject It is the species found in 95 per cent of actinomycotic mycetoma due to aerobes in Mexico

It is readily cultivated Growth begins on the sixth day on Sabouraud's 2 per cent dextrose medium at laboratory temperature, with the appearance of white, opaque points After a time, the colony has the appearance of an acuminate disc, with wrinkled surface, with tendency to form radial folds It appears dry The color varies from yellowish to orange red, with white powdery zones The mycelium has an average diameter of 0 7 micron and fragments into coccoid and bacillary elements, the tendency toward fragmentation varying according to the strain It is partially acid fast and enzymatically active

Nocardia brasiliensis (Lindenberg, 1909) Castellani and Chalmers, 1913, predominates in Brazil and has the same characteristics as *N mexicana* Despite the fact that, according to our criteria, *mexicana* is the same as *brasiliensis* (González Ochoa, 1945), we shall be conservative and mention these 2 species separately until such time as other authors corroborate our hypothesis

Nocardia madurae (Vicent, 1894) Lachner Sandoval, 1898, was first isolated in Africa and has been noted in all tropical and subtropical countries, under various names It develops better at 37° C. It is of slow and meager growth, with heaped, wrinkled, moist colonies, whitish ivory to cream colored, waxy in appearance, which in successive transplantations and according to strain become pinkish, especially when cultivated at a temperature of 37° C.

The colony is very adherent to the medium, as opposed to *N. pelletieri*, with which it is easily confused when the strain is pigmented. It does not present fragmentation and is not acid fast. It is enzymatically active.

Nocardia pelletieri (Laveran 1906) Pinoy, 1912. This name was created for the fungus of mycetoma with red granules found in Senegal. No culture was made in this case. Thiroux and Pelletier (1912) isolated an actinomycete from a second case of red granule mycetoma and called it *A. pelletieri* of Laveran. It is frequently found in India and Egypt and on rare occasions has been isolated in widely different countries. Its origin is confusing. Nocardiae causing mycetomas with red granules and which grow into ruby colored colonies are classified as *N. pelletieri*.

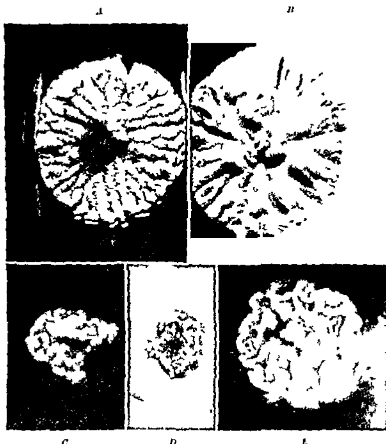


Fig. 393. A, Colony of *Nocardia mexicana*; B, colony of *N. brasiliensis*; C, colony of *N. madurae*; D, colony of *N. pelletieri*; E, colony of *N. asteroides* in Sabouraud's 2 per cent dextrose solution.

On Sabouraud's 2 per cent dextrose medium the fungus produces small heaped cerebriform moist and very soft colonies slightly adherent to the medium and usually of a beautiful coral pink to red color. With successive transplantations they lose this hue and become pink or orange. They do not show *fragmentation* and are *not acid fast*. They have enzymatic activity.

Nocardia asteroides (Eppinger 1891) Blanchard 1896 has been found in cerebral abscesses, diffuse peritonitis, pulmonary mycoses and very rarely in mycetoma of the limbs.

It shows great morphologic variations, as well as variations in the pigment of the colonies The colonies are usually soft, moist, glabrous, and wrinkled The color varies from yellow to ochre and red They are verrucose or finely granular, rarely with white, powdery zones The filaments are more slender than those of other aerobic Actinomycetales, being 0 3 to 0 5 micron, and show a decided tendency toward fragmentation, resulting especially in coccoid elements The fungus is partially acid fast and lacks enzymatic activity Some strains are pathogenic for guinea pigs

Other Aerobic Mycetoma-Producing Actinomycetales —In addition to the above species, the validity and frequency of which are generally accepted, there are others which, although valid, have been isolated but once

A great number of species exist, but we find no reference to them since no specimens are found in mycologic collections and descriptions of them are so incomplete that we can not judge the validity of the species *

Maduromycotic Mycetoma Maduromycosis

Just as in the etiology of actinomycotic mycetoma, the maduromycotic type is also studied according to color of the granules, although as before, color is not constant in the same species In maduromycosis the frequency of black granules is approximately equal to that of the white yellowish varieties, there are also red granules, although these are extremely rare.

Fungi isolated from maduromycotic mycetoma belong to fungi imperfecti and Ascomycetes

Among the first, the principal genera are Madurella, Monosporium, and Cephalosporium In the Ascomycetes, the genera are Aspergillus, Penicillium, Sterigmatocystis. They are not so frequent Almeida and Simoes Barbosa (1940) reported that, in addition to the genera mentioned, Acremonium and Candida have been observed in Brazil

There is some confusion with respect to the etiologic agents of maduromycotic mycetoma We shall not attempt to give all the fungi which have been described as the cause of this condition, since botanical knowledge concerning them is very limited, classification is arbitrary, and descriptions taken from authors who have isolated them are to a great extent incomplete There are such fungi as *Torula jeanselmei* which, because of their rarity, will not be discussed We shall confine ourselves to the genera Madurella, Monosporium, and Cephalosporium, the frequency of which, as well as proved data, justify their mention

Madurella Brumpt, 1905 —Some 8 species are included in this genus The most frequently found is *M mycetomi* (Laveran, 1902) It has been isolated in India, North and West Africa Madagascar, Brazil, Argentina, and other countries of South America The granules are very hard, dark, verrucose, and filamentous and may be included in an interstitial substance Cultivation of *M mycetomi* is difficult, and the colonies develop slowly They are very dark brown and discolor the medium According to Langeron (1936), no sporiferous apparatus has been described in this fungus, so that its group is unknown Arthrospores have been described The remaining species of Madurella have been even less studied.

Monosporium Bonorden 1851 —According to modern mycologic classification, species placed formerly in the genus Scedosporium are to be placed in the genus Monosporium. This genus produces whitish yellow maduromycotic granules The principal species is *M apiospermum* Saccardo, 1911 It has been isolated in Brazil, Algeria, Tunisia, and Morocco, where it is very frequent, also in Puerto Rico, the United States and Italy The fast growing colony is cottony, with tuft like aerial growth which turns gray A black pigment penetrates the agar Microscopically, ramified, septate hyphae can be seen, 1 to 3 microns in diameter,

*Editor's note (O F) *Nocardia paraguayensis* (Almeida) Conant 1947 forms glabrous, dark cream colored colonies with white center adherent and darker, projecting border is not acid fast, does not show fragmentation of the mycelium The granules in the tissue are black with clubs

anastomosed to form bundles of hyphae (coremia) Fertile hyphae are not differentiated from vegetative hyphae Conidia are pyriform or oval, 6 to 10 microns by 3 to 8 microns, and appear along the side of the conidiophores or at the end Generally they occur singly, rarely forming groups of 2 to 4 elements

Cephalosporium Corda 1839 —Species belonging to this genus have been isolated in Brazil, Puerto Rico, Mexico, and the United States Some have been described simply as *Cephalosporium* sp while others have been given definite names so that we have *C recifei* Leao and Lobo, 1934, and *C granulomatis* Weidman and Klingman, 1945 Colonies are filamentous tufted or appear like locks of hair generally white or rose colored Microscopically they show septate ramified filaments grouped in coremia 2 to 4 microns in diameter, with straight or curved conidiophores of varying length with agglomerations of conidia at the ends These are fusiform elongated 5 to 6 microns by 0 5 to 1 0 micron, straight or falciform.

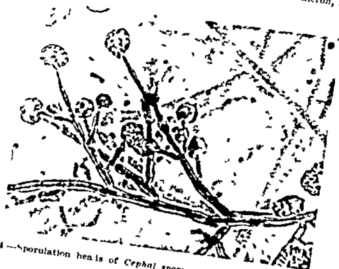


Fig 394 —Sporulation heads of *Cephalosporium* sp isolated from mycetoma.

LABORATORY DIAGNOSIS

The clinical data suffice to indicate a diagnosis of mycetoma in the greater number of cases However, there are cases in which only a laboratory diagnosis can furnish the clue and microscopic study of the granules is necessary in every case to ascertain that the disease is a mycetoma The granules must also be studied to differentiate maduromycotic from actinomycotic mycetoma

Laboratory diagnosis includes direct examination culture and histologic study

Direct Examination.—Granules or secretions from fistulae are procured in the manner outlined above and examined microscopically in a drop of Lugol solution It is best to use the low power dry objective since in the great majority of cases the granules are large enough to be easily seen They appear as round and kidney shaped, or lobulated with intensely stained outline Under high power the 2 zones may be seen the central zone and the zone of the clubs the characteristics of the first being different for actinomycotic and maduromycotic granules

Culture—Cultures are grown on Sabouraud's 2 per cent dextrose agar at laboratory temperature The aerobic Nocardia, as well as the different fungi of marudomycotic mycetoma, develops under these conditions *The identifying characteristics of the principal species which cause mycetoma are given above*

Biopsy.—There is no definite histologic picture in mycetoma, and only the finding of granules permits a diagnosis The histologic reaction to these fungi is described above

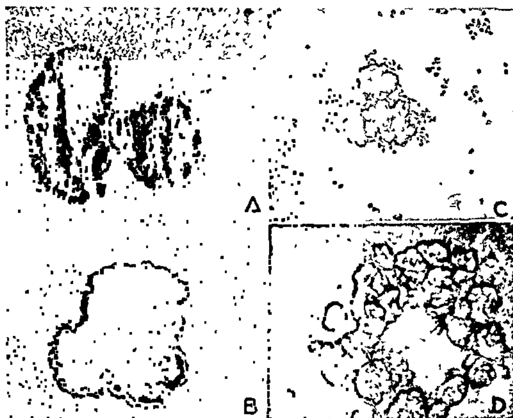


Fig 395—Granules of mycetoma observed by direct examination A maduromycotic granule B, actinomycotic granule C and D actinomycotic granule formed by agglomeration of many small granules

Animal Inoculation—These fungi are practically not pathogenic to laboratory animals Some authors have reported successful inoculations, but these are open to doubt, since they could not be repeated by other workers. Of the aerobic Actinomycetales, only some strains of *N asteroides* are virulent for guinea pigs and rabbits (Drake and Henrici, 1943), with death due to formation of actinomycotic granules in the tissues The various fungi of maduromycotic mycetoma, as well as other aerobic Actinomycetales, produce only foreign body reactions following inoculation, which tend to cure promptly

Hematology—In most of the advanced cases there is an increase in the sedimentation rate, moderate leucocytosis (10,000 to 12,000), neutrophilia, and decrease in the number of erythrocytes Marked changes in the blood picture are those ordinarily seen in bacterially infected cases and possess the characteristics of the added infection

Immunology—Only tests of academic value have been published, demonstrating the fact that in the blood of patients with mycetoma there are antibodies which may fix complement No standard antigens have been prepared for the test Blood serum of patients precipitates extracts of the etiologic fungi In rabbits infected with N asteroides, an allergic state can be demonstrated with extracts of the fungus or proteins and purified polysaccharide extracted from the microorganism (Drake and Henrici 1943)



Fig 396 — Actinomycetic granule lodged in an abscess

TREATMENT

Treatment varies according to the stage of the disease and upon invasion or lack of invasion of the bone Many different treatments have been proposed in the literature indicating their lack of usefulness Potassium and sodium iodides are indicated some authors consider these as specifics while others deny their usefulness Without attempting to review all the proposed medications we can state only that none from thymol to x rays have given beneficial results in the many cases in which we have used them

After reading various publications which appeared since Walker (1938) spoke of the curative action of sulfanilamide in infections due to A bovis, we carried out in vitro experiments to learn whether or not pathogenic Actinomycetales are also susceptible to sulfonamides We found that N asteroides was completely inhibited by sulfanilamide in a concentration of 1 5 000, and showed partial inhibition even with a concentration as weak as 1 40 000 (Gonzalez Ochoa and Zozaya, 1942) Later we saw that the combined treatment of

sulfonamides and iodides gave good results in 2 cases of pulmonary infection by *N asteroides* This work was done by Benbow Smith and Grimson (1944)

A practical form of administration of this treatment consists in giving daily approximately 4 Gm of sulfanilamide sulfathiazole or sulfadiazine preferably the last divided equally over a 24 hour period with 1 day of rest per week Treatment should be administered with all due caution and continued for as long as it is necessary to effect a cure (from 2 to 6 months) It must be discontinued if any toxic signs appear At the same time we prescribe potassium iodide beginning with 0 50 Gm and increasing the quantity daily until 4 to 5 Gm are reached divided into 3 doses a day it is dissolved in milk and taken promptly after each meal

If this treatment is tolerated by the patient good results may be obtained under the stated conditions We have observed that when treatment is suspended for several days and then renewed the initial beneficial results are no longer obtained so that it is important not to discontinue treatment if it is well tolerated by the patient

In very advanced cases in which invasion of the bone generally exists the treatment is not effective and only amputation may control the disease It is important to amputate sufficiently high above the infected area If the surgeon is too conservative the infection may reappear in the stump and this time the mycetoma assumes a more active or invading form in the latter case all hope of surgical intervention is lost It is not a rare occurrence to observe that in mycetoma of the knee if amputation is carried out in the median part of the thigh it may be necessary later to carry out disarticulation of the reinfected stump mycetoma of the abdomen follows with invasion of the pelvis

All usual measures for fortifying the patient s defenses are recommended blood transfusion rest vitamin therapy etc

In summary it may be stated that in the absence of invasion of the bone the combined treatment of sulfonamides and potassium iodide affords hope of cure In cases of invasion of bone the indicated treatment is advised improvement and even arrest of the process in not very active cases may be obtained but it must be kept in mind that surgical excision must be carried out far enough above the diseased tissue to get rid of the mycetoma

The aerobic actinomycetes are not susceptible in vitro to penicillin and streptomycin The sulfone drugs are active against them but to a lesser degree than sulfonamides *

CHROMOBLASTOMYCOSIS†

Synonyms —Dermatit s verrucosa and chromomycos s

Chromoblastomycosis has only recently been studied with the first case published in 1915 It is found universally although it definitely predominates in the tropics Its correct name is still under discussion although the gen

*Editor s note (O F) Recently antibiotics have been found effective The choice of them depends on the causative agent

†See also Chapter 51

erally accepted name is chromoblastomycosis It is believed to be quite a common infection since, shortly after it had been identified, the disease was reported from many different regions

DEFINITION

Chromoblastomycosis is a decidedly chronic affection with nodular cutaneous lesions of varied appearance, although fundamentally of a verrucose and papillomatose aspect It is generally localized in the lower limbs It may be caused by 3 species of fungi *Hormodendrum pedrosoi* *H compactum*, and *Phialophora verrucosa*

HISTORY

Lane, in 1915 described a new cutaneous disease in the United States, caused by a fungus which was classified by Medlar (1915) as *Phialophora verrucosa*

The first observation in South America was made by Pedroso in São Paulo in 1911 and later reported by Pedroso and Gomes The disease was named "blastomycosis nigra" when published in 1920 The agent was identified as *P verrucosa*. The culture obtained from the first Brazilian case was studied by Brumpt who placed the fungus in the genus *Hormodendrum* His work was not published until 1922, the fungus was then given the name *Hormodendrum pedrosoi*

Since the Brazilian cases differed from those observed in the United States, and since the organisms which had been isolated also differed the diseases were thought to be dissimilar *P verrucosa* was later isolated, in Brazil from cases which were clinically identical with the first and cases due to *H pedrosoi* which were very similar to those produced by *P verrucosa* were found in the United States This led to the conclusion that there were several types of clinical appearances of chromoblastomycosis and that it was produced by 2 different fungi *Hormodendrum pedrosoi* and *Phialophora verrucosa* It has since been proved that only one nosologic entity with different clinical aspects, is involved. To the causal agents has been added *H compactum* isolated by Carrión (1935) in Puerto Rico

SYMPTOMATOLOGY

Lesions are limited to the skin and the subcutaneous tissue They are generally localized on the lower limbs the foot and leg, less frequently on the upper limb although lesions may be found in any part of the skin They have been observed in such areas as the gluteal region the face, neck etc Lesions may be verrucose papillomatous sometimes ulcerated of a slow chronic development Cases of 40 years duration have been described

Prognosis is good It is not a painful condition but it is sometimes accompanied by slight pruritus The fungus does not invade deeper structures and does not become generalized It appears to spread by continuity, with the exception of 2 or 3 cases with metastases but in these the possibility of autoinoculation must be considered

The disease begins with a papule or nodule sometimes with a verruga which in certain cases ulcerates and becomes covered by papillomatous crusts Later, additional warty growth appears similar to the first Through confluence of these elements, irregularly scattered vegetations result which may cover large areas even the whole limb The verrucose vegetations in some cases resemble dirty gray cauliflower In some sites pus accumulations with a marked putrid



Fig 397 —Chromoblastomycosis verrucose type showing hypertrophic and hyperkeratose zones some isolated others forming large plaques (Photograph of González Chávez)



Fig 398 —Lesions of chromoblastomycosis simulating tuberculosis verrucosa cutis

odor are observed In others there is spontaneous remission leaving atrophic retracted white scars The edges of the lesion are generally well defined and are surrounded by normal skin There are no lymph gland reactions except those due to secondary infection The disease does not attack the general health of the patient but produces invalidism due to the great hyperkeratosis Sometimes elephantiasis develops



Fig 399—Chromoblastomycosis syphiloid type Lesion consists of serpiginous erythematosquamous zones simulating an old syphiloderma (Photograph of González Chávez)

Pardo Castello et al (1942) discussed the clinical manifestations found in 31 cases observed in Cuba They divided these into 5 different types verrucose tuberculoid syphiloid psoriasiform and cicatricial and elephantiac as follows

Verrucose or Papillomatous.—This type is the most frequently found It is commonly localized on the lower limbs as elevated hyperkeratotic, hypertrophic zones which may form isolated patches 5 to 7 cm in diameter or large confluent masses These zones are made up of small nodules or papules which are scaly in the beginning later hypertrophy and produce verrucose zones The color varies from light brown to dark red depending upon the quantity of keratotic material accumulated on the surface When keratosis is not pronounced the zones tend to be reddish and soft In newly formed lesions there is a collection of yellowish white thick or fluid sometimes sanguineous or fetid

pus This is due to secondary infection Sometimes frambesia like zones rise abruptly on an apparently normal skin, or inflamed and cicatricial areas form between the hypertrophic masses, giving the appearance of verrucose rings The lesion is usually unilateral and may extend over the entire limb, or it may be limited to an area of a few centimeters

Tuberculoid—This type is similar in appearance to tuberculosis verrucosa cutis or sarcoid The lesions are usually limited to hypertrophic nodules with erythematous and slightly scaly areolas In most cases clinical differentiation from tuberculosis verrucosa cutis and sarcoid may be very difficult Laboratory investigations alone may identify the disease This form may be less chronic than the verrucose type



Fig 400—Extensive zones of verrucosities and atrophic cicatrices in a greatly enlarged leg the cicatricial and elephantiac type of chromoblastomycosis (Photograph of González Chávez)

Psoriasiform—This form is thought to be rather rare It consists of one or several flat "plaques" of inflammatory superficial infiltration covered with shiny, very adherent scales similar in appearance to areas of psoriasis, however, the lesions are not symmetrical and do not bleed easily when scratched When the scales are removed, short papillary projections may be observed under them There are no verrucosities or abscesses in this clinical form

Syphiloid.—In this clinical type the lesions are scarce and are sometimes restricted to only one group They are formed by small, flat, scaly, and slightly erythematous nodules which are grouped in rings or in a serpiginous form, which may ulcerate, simulating old syphiloderma or syphilide The lesions progress excentrically, leaving depigmented atrophic scars No warts are observed, but rusts cover the ulcerations

Cicatricial and Elephantiac Type.—This clinical type is found in the legs The lesions are very extensive and are formed by verrucose zones and zones of atrophic cicatrices due to the spontaneous healing of the warts as well as disseminated ulcerations and abscesses The leg increases greatly in size in some parts, usually in the foot, and takes on the characteristic appearance of "mossy foot" due to the accumulations of dirty blackish growth and keratotic material This elephantiasis is due to stasis in the lymphatic circulation and fibrosis It represents the final stage of some verrucotic types with a tendency to fibrosis

GEOGRAPHIC DISTRIBUTION

Chrombolastomycosis is a cosmopolitan disease, although it is more frequently observed in tropical and subtropical regions A large number of cases have been described in Brazil Puerto Rico, and Cuba It has been observed in the United States, as well as in Canada, Argentina, Uruguay, Paraguay, Venezuela, Panama Costa Rica, Santo Domingo, Guatemala Colombia, and Mexico It has also been reported in European Russia, Japan, Rhodesia Algeria, and the Union of South Africa, Netherlands, East Indies, and Australia

EPIDEMIOLOGY

Incidence.—There are only 151 cases reported (Carrion and Silva 1947)

Age.—Most cases are observed between the ages of 30 to 50 years The lowest observed age is 12 years and the highest 77 years

Sex.—It is noteworthy that this disease is seen almost exclusively in males There are only 4 cases of chromoblastomycosis in females in the literature

Race.—Rural inhabitants are particularly affected perhaps due to greater contact with vegetation, also to the custom of not wearing footgear

Endemicity.—There are no defined endemic zones The fact that numerous cases have been described in certain geographic regions such as Sao Paulo, Puerto Rico, and Cuba may be due to the greater interest in this disease in these places

ETIOLOGY

The fungi which cause chromoblastomycosis, just as those which produce other deep mycoses differ morphologically in the parasitic state (organism which attacks) from the parasite in the saprophytic state (culture) In the human body the fungus takes the form of rounded cells, single or in groups of a brown color, sometimes septate, and with a thick wall The size varies in tissue, exudates, and scales from 5 to 15 microns These elements are known as "sclerotic cells" of Medlar

In a histologic section they are observed in small abscesses, in giant cells,' and among connective tissue cells Sometimes they appear corrugated

In the pus and especially in the scales where they are more readily observed they present the characteristics described above except that they are larger, sometimes as large as 30 microns Frequently septate filaments are observed growing out from these cells

At the present time it is accepted that chromoblastomycosis may be caused by 3 kinds of fungi *Hormodendrum pedrosoi* Brumpt 1922 *Phialophora verrucosa* Medlar 1915 *Hormodendrum compactum* Carrión 1935 The same mycologic elements in the parasitic state are observed in all of these species the sclerotic cells of Medlar There is no appreciable difference in the clinical modality in relation to the causal species

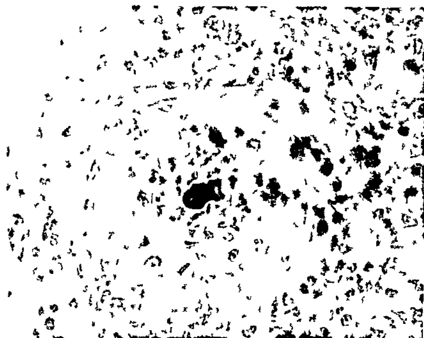


Fig 401—Parasite of chromoblastomycosis in a histologic section

Cultures are easily obtained in the media generally used in mycology On Sabouraud s 2 per cent dextrose medium the development of these fungi begins approximately on the eighth day with the appearance of small blackish accumulations which when they mature are morphologically little different in the 3 species Cultures show filaments and conidia in special groupings the colony has a downy appearance dark olive green to dark brown

Hormodendrum pedrosoi—This fungus, the most frequent cause of chromoblastomycosis has been isolated in all regions where this mycosis has been seen The colonies resemble a heaped disc with a central protuberance or mammilla The surface is downy, from gray with a greenish tint to dark olive green or blackish brown Beneath the downy surface is a compact base blackish of muddy appearance which may be observed by withdrawing a portion of the colony with a platinum loop

Microscopically are observed filaments, rectilinear or slightly undulant ramified with thick partitions which separate parts of varying lengths containing a greenish brown protoplasm. They vary from 2 to 4 microns in diameter The reproductory apparatus is formed by conidiophores of various lengths, and chains of conidia, simple or ramified the latter

show ng aborescence Conidia establ sh contact with each other by means of small prominences or a th cken ng in the membrane called disjunctors Conid a are joined to the conidiophore by means of an elongate l cell hich son et n es l as the appearance of a shield and in which the d sjunctors are more apparent Th s cell sometimes septate is called tle primary

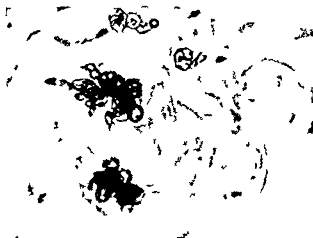


Fig 402 — Sclerotic cells of Me l ar s en in scales in d rect ex n nation as roun le l par t tioned form lso ate l or n groups



F g 403 —A and B Paras tic a p t of Horn odendr m ped osoi In a l lit on to dark rounde l ce s th re are wal e l fil ments start ng f m these

element Tl ey vary from 4 to 8 m crons in leng h by 2 to 3 m rons in width The first con d a are somet mes oval ten l ng to l ecome spl er cal as they grow away from the pr mary element and decr as ng somewhat in s ze Tl ey are 2 to 3 n crons l y 3 to 5 microns Their color is green sh l rown or ol ve gre n They break down read ly and are eas ly separated from the r character t c group ng

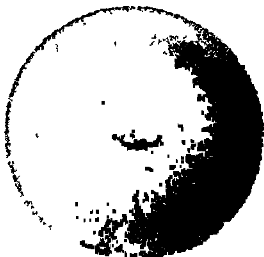


Fig 404 —Colony of *Hormodendrum pedrosoi* in Sabouraud's 5 per cent dextrose solution.

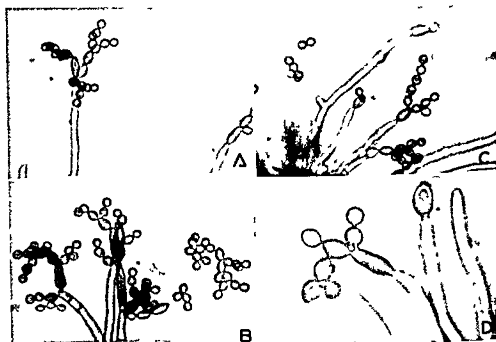


Fig 405 —*A D*, Sporulation Hormodendrum type in *Hormodendrum pedrosoi*.

In addition to the above type of sporulation called "Hormodendrum" type, the "Acrotheca" or "Fonsecaea" and "Phialophora" types may be found, dependent upon the different strains and the culture media in which they are grown

In the "Acrotheca" or "Fonsecaea" type of sporulation, the spores form at the end, or at the sides of the swollen, club shaped conidiophore

The "Phialophora" type, which will be described in more detail when discussing the species *P verrucosa*, is characterized by the production of semiendogenous conidia from flask shaped conidiophores with terminal cups This form of sporulation has been demonstrated by Emmons and Carrión (1936) in *Hormodendrum pedrosoi*, indicating the close relationship



Fig 406—Sporulation Acrotheca or Fonsecaea type of *Hormodendrum pedrosoi*

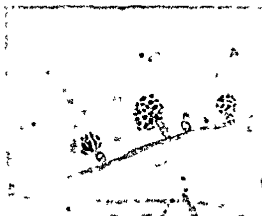


Fig 407—Sporulation Phialophora type of *Hormodendrum pedrosoi*

which exists between *H pedrosoi* and *P verrucosa*, although they are considered as belonging to different genera This similarity of sporulation has resulted in a suggestion by several authors that the fungi be included in the same genus Binford, Hess, and Emmons (1944) suggested that the genus Phialophora be extended to include the 3 species described as causal agents of chromoblastomycosis, these would then be named *P verrucosa*, *P pedrosoi*, and *P compactum* Until such time as this suggestion is generally accepted, continued use of the classical terminology will prevent confusion.

Carrión and Silva (1947) described 4 varieties of *H pedrosoi* according to the various proportions in which the 3 types of sporulation may be represented in different strains The

varieties are variety *typicus*, with "Fonsecaea" type most highly developed, "Hormodendrum" scant and "Phialophora" rare, var *cladosporioides*, in which "Hormodendrum" sporulation is highly developed "Fonsecaea" scant, and "Phialophora" rare, var *phialophorica* with Phialophora" sporulation predominant, "Fonsecaea" scant, and "Hormodendrum" absent, var *communis*, the most frequent variety, in which sporulation of "Hormodendrum" and "Fonsecaea" types are always abundant, but "Phialophora" type is scant

Hormodendrum compactum Carrión, 1935—This species is similar to *H pedrosoi*, it has been isolated only twice, from one case in Puerto Rico and another in the United States Armed Forces in Tennessee Three types of sporulation are found, just as in *H pedrosoi* The dominant form is the "Hormodendrum" type, while the "Fonsecaea" type is not conspicuously abundant and the Phialophora" type is scant



Fig 408—Colony of *Phialophora verrucosa* in Sabouraud's 2 per cent dextrose solution.

H compactum differs from *H pedrosoi* by having shorter and broader, subspherical, not readily dissociated, and more compactly grouped conidia, without "disjunctors" The culture develops more slowly It is roughly conical and of a dark olive green color Its border is irregular and indented

Phialophora verrucosa Medlar, 1915—This species produces somewhat conical colonies which grow slowly, like those of Hormodendrum, dark brown or blackish, with a fine velvety or felt like olivaceous or gray aerial mycelium There are great variations in the color of the colonies and in the size of spores

Under the microscope, short conidiophores may be observed sprouting laterally or terminally from the mycelium near the partitions They are cup shaped or flask shaped (phialides), 3 to 4 microns in diameter by 4 to 10 microns in length The conidia are produced singly within the conidiophores or phialides by a process similar to budding, and when they emerge they are retained in groups by a mucilaginous substance, forming rounded accumulations at the orifice of the phialide Conidia are oval, 2 microns wide by 4 microns long

P. verrucosa presents only the type of sporulation described It is found less frequently than *H pedrosoi* as a cause of chromoblastomycosis and has been isolated in the United States, Algeria, and Uruguay

Reproduction—The appearance of the parasites in the tissues in the form of septate cells suggests that its reproduction is by cellular division and not by budding Upon this fact is based the opinion that the name *chromoblastomycosis* is incorrect, since this name suggests that the causative fungus reproduces by gemmation

LABORATORY DIAGNOSIS

Diagnosis is readily made in most cases Three methods are used direct examination, culture, and biopsy

Direct Examination—Scales, pus, or thin sections of corneous material obtained with a razor blade are placed between slides in a drop of 10 per cent potassium hydroxide or in Amann s chlorolactophenol This preparation is carefully heated until bubbles begin to appear, then observed under the high power objective, since the parasitic elements are about 10 microns in diameter

All species which produce chromoblastomycosis will be seen as rounded, dark brown cells, sometimes septate, frequently with a double wall In some patients short filaments are seen at the side of the partitioned cells, or emerging from them These are also brown

Culture—The same material used in the direct examination, or fragments of affected tissue, are seeded on Sabouraud's 2 per cent dextrose medium, and the tubes are kept at laboratory temperature We have obtained good results by passing the parasitized cells through alcohol for a few minutes before inoculating the culture medium, as suggested by some authors, to prevent bacterial contamination Growth begins on the sixth to tenth day and takes the form of blackish accumulations which later assume the morphology described above

Biopsy.—The diagnosis of chromoblastomycosis is frequently made by biopsy in conditions which had been mistaken for tuberculosis or syphilis In small abscesses or within giant cells, rounded brownish cells may be seen These are the parasitic elements In some cases it is difficult to find the parasite so that a large number of sections must be examined before chromoblastomycosis is eliminated from consideration

Inoculation of Laboratory Animals—Among the different animals tested to reproduce the disease, rats and mice are the most susceptible to infection with *H pedrosoi* and *P verrucosa* The infection may be effected by the intraperitoneal, the subcutaneous, and intratesticular routes

Hematology—There are no hematologic changes due to the presence of the fungus in tissues Leucocytosis, anemia, and other anomalies of the blood presented by some patients are due to accompanying infections

IMMUNOLOGY

As in other deep mycoses, the subject of immunology has scarcely been touched In chromoblastomycosis the necessity of immunologic tests for diagnosis is less than in other mycoses since lesions are not in the viscera or in accessible places, but are exclusively cutaneous, and direct examination and culture and biopsy are sufficient to identify the mycosis

Complement Fixation —Conant and Martin (1937) demonstrated that the serum of rabbits immunized with *H pedrosoi* and *P verrucosa* contains specific complement fixing antibodies Conant et al (1944) noted that the serum of a subject infected with *H pedrosoi* fixed complement with antigen prepared from the causative fungus as well as with antigens from various strains of the same species and of *P verrucosa* The reaction was negative with antigens from other pathogenic fungi such as *B dermatitidis* and *S schenckii* and from saprophytic species of Hormodendrum

Intradermal Reaction —Very few data exist concerning cutaneous reactions with antigens prepared from the etiologic agent Baliña et al. (1932) reported a strongly positive reaction in a patient suffering from chromoblastomycosis using a mixed antigen of *H pedrosoi* and *P verrucosa*



Fig 409 —Histologic section from a case of chromoblastomycosis showing parasites within rete pegs layer and microabscess

PATHOLOGY

There is a uniform criterion concerning tissue reaction which determines the presence of the fungus however one must insist that mycosis can be diagnosed only by finding the parasitic elements Almeida (1939) Pardo Castelló et al (1945) Simson (1946) and others report acanthosis and hyperkeratosis as the most constant lesions of the epidermis in the cutis are numerous small abscesses formed by polymorphonuclear neutrophilic leucocytes sometimes eosinophiles and giant cells some of which contain parasites The lesions are granulomatous with pseudotubercles

In all clinical types there is acanthosis more noticeable in the verrucose and papillomatous cases Hyperkeratosis and parakeratosis are common Sometimes epithelial hyperplasia is very great and the interpapillary columns penetrate deeply into the cutis and intraepithelial abscesses may be present The parasite which is more frequently found in the cutis may be seen in the hyperplastic epidermic covering within the abscess

The corium is greatly thickened with polymorphonuclear neutrophilic cell infiltration with parasites frequently seen between them There are also lymphocytes epithelioid cells and giant cells (pseudotubercles) Plasma cells and Russell bodies are frequently seen The miliary abscesses may take on a tuberculoid aspect with epithelioid cells and lymphocytes surrounding giant cells of the Langhans type Around them are seen infiltrates with poly morphonuclear neutrophiles lymphocytes eosinophiles and plasma cells

Simson (1946) considers the inflammatory process which results from the presence of the fungus to be basically a reticuloendotheliosis and that the most characteristic part of this process is the formation of 2 types of nodules within unspecific inflammatory tissue The nodule most frequently observed is composed of reticuloendothelial cells and at times contains certain giant cells which may or may not contain parasites The other type consists of a central area of polymorphonuclear neutrophiles surrounded by a zone of reticuloendothelial cells The nodules of chronic lesions resemble tubercles but the absence of acid fast bacilli and especially the presence of the infecting fungus are diagnostic

PROGNOSIS

Chromoblastomycosis is not a fatal condition Advanced or very chronic cases are not curable In localized lesions and in the beginning of the dis ease adequate treatment may result in its disappearance

TREATMENT

When the lesion is incipient and therefore restricted treatment by electro coagulation or surgical excision should be carried out

As in many of the deep mycoses sodium or potassium iodide produces marked improvement but without effecting a cure As noted by Carrion and Koppisch (1939) we have also observed marked alleviation of the symptoms after intense and prolonged iodide treatment but we continued to find the parasites in the scales and in the tissue and were able to obtain cultures of the fungus

Martin Baker and Conant (1936) stated that they had obtained excellent results by iontophoresis with copper sulfate

Pardo Castello et al (1942) reported success with roentgen therapy in superficial or slight cases Doses employed by these authors were of 600 to 1200 r filtered through aluminum with 1 2 mm filters depending upon the size of the growth

Calero (1946) had success in one case with roentgen therapy and in an other by surgical electrocautery

Sulfonamides and their derivatives have been tried without favorable results (Pardo Castello et al 1942)

The treatment of choice should be a combination of all useful agents especially electrocoagulation of the lesions together with intensive iodide treatment It must be remembered that iodides are useful only as a long term treatment

SOUTH AMERICAN BLASTOMYCOSIS

South American blastomycosis is discussed in Chapter 51 and will not be repeated here

RHINOSPORIDIOSIS

The causal agent of rhinosporidiosis was once thought to be a protozoan The disease at present is considered a mycosis although the organism has not been cultivated as yet

DEFINITION

Rhinosporidiosis is an affection characterized by the production of polypoid tumors of the mucosa of the nose pharynx eyes ears occasionally of the penis vagina and rectum and at times of the skin It is caused by a fungus *Rhinosporidium seeberi*

HISTORY

Malbrán (1892) observed for the first time in Argentina parasites encapsulated in a nasal polyp These were believed to be protozoa The observation was not reported until Seeber in 1900 published a study of 2 cases of nasal polyp caused by a parasite similar to that observed by Malbrán and which Wernicke classified as a protozoan naming the organisms *Coccidium seeberi* A few years later O Kinealy (1903) presented before the Laryngological Society of London material consisting of nasal polyps from a patient in Calcutta The parasite observed was called *Rhinosporidium kinealyi* by Minchin and Fantham (1905), who placed it among the Haplosporidia and later considered it to be identical with the parasite of Malbrán and Seeber

In 1923 Ashworth suggested that the true nature of the parasite was that of a yeast this belief is unanimously held at present

GEOGRAPHIC DISTRIBUTION

The disease is frequently found in India and Ceylon although sporadic cases have been described in different regions It has been recorded in Argentina Paraguay Uruguay Brazil the United States Italy England the Malayan States Persia Uganda and the Philippines

EPIDEMIOLOGY

Occupational Incidence—The disease appears often in individuals who work or swim in stagnant water Conant et al (1944) stated that a 20 per cent incidence was found by Mandlick in a group of laborers whose occupation was removing sand from a stagnant river

Race—There is no racial predisposition

Age—Cases ranging in age from 5 to 85 years have been found but the infection is most frequent during the active age of life

Sex—Men are much more frequently affected than women Karunaratne (1936) stated that of 231 cases collected by him 202 were men

Source of Infection—The fungus which causes rhinosporidiosis has not been found in nature The majority of those who have studied the disease suggest that possibly the parasite lives in water perhaps infecting certain fishes This hypothesis is supported by the occupational incidence Some authors believe that infection is acquired by contact from animals (horse and mule) in which rhinosporidiosis has been observed, however this mycosis does not predominate among farm and ranch workers *

SYMPTOMATOLOGY

The disease is manifested by polypoid proliferations The affected sites in order of frequency are the nose where the largest number of cases are observed (72 per cent in 280 cases reported by Karunaratne 1936) then the eye the nasopharynx and last the ear penis vagina rectum and skin these last localizations being rare

The polyps are sessile or pedunculated rose colored to deep red the surface covered with papillary projections giving a raspberry like appearance or with cauliflower like verrucosities when the tumor is old The tumor like formations are covered with sticky mucus and bleed upon the slightest injury In the beginning while small they are flat later becoming pedunculated Upon close observation small whitish spots may be observed underneath the epithelium which covers the polyp these are the parasites (sporangia) Frequently rupture of the epithelium permits these mycologic elements to pass into the mucus covering the growth

The condition in general is not painful and does not affect the patient's general health Its development is eminently chronic and does not tend to heal spontaneously Metastases have not been reported

CLINICAL FORMS IN RELATION TO SITE OF INFECTION

Nose—As stated above this localization is the most frequent Lesions appear on the septum at the junction of the cartilaginous and osseous portions the right side of the nose being more often affected (Caldwell and Roberts 1938) The lesion begins with a marked pruritus and abundant discharge of mucus which only rarely is bloody or purulent At this stage a small flat growth appears which becomes pedunculated and lobulated as it grows and may finally protrude from the nose hanging in front of the mouth and obstructing the nasal cavity When the tumor extends backward toward the nasopharynx difficulty in breathing and swallowing develops

Eye—Incidence in this localization is 14 per cent (Karunaratne 1936) The disease appears on the palpebral or bulbar conjunctiva In the beginning it presents small, flat rose colored papules Later these become lobulated and their color darkens Symptoms of a foreign body irritation appear, such as

*Editor's note (O F) Manson calls attention to the fact that *R equi* is closely related to *R seeberi*

photophobia, lacrimation, reddening of the conjunctiva Infection of the tear sac is rare, but when it does occur, produces obstruction which results in excessive lacrimation *

Nasopharynx—The appearance is similar to the nasal polypoids The tumor is lobulated, pedunculated, and covered with mucus Symptoms due to obstruction—difficulty in breathing and swallowing—are more accentuated in such cases

Skin, Ear, Penis, Vagina, Rectum—These are infrequent sites of infection by *R seeberi* On the skin, the disease appears as a verrucose papilloma, usually not painful In the ear, it resembles a nonspecific polyp On the penis, vagina, and rectum, it has the appearance of venereal condyloma, in the rectum, it is easily confused with rectal polyps and hemorrhoids

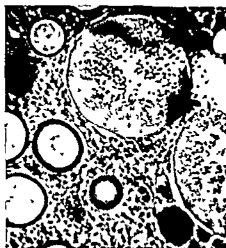


Fig 410—*Rhinosporidium seeberi* Biopsy from nasal mucosa showing different stages of development The black spots show fully capsulated and undivided organisms (Courtesy of Oscar Felsenfeld)

ETIOLOGY

The parasite is found within the tumor It is cyst like, of variable sizes and shapes

Two elements are seen, the sporangium and the spore Sporangia are cystic forms, attaining as much as 300 microns in diameter, with a chitinous membrane, sometimes striated, they contain thousands of spores The spores are the daughter spores in the sporangia They are 5 to 9 microns in diameter, with a chitinous cover, vacuolated cytoplasm, and a large vesicular nucleus with a karyosome

According to Ashworth (1923) the parasite develops as follows the daughter spore emerging from the sporangium develops in the sinuses of tissue and, as it grows granules appear in its cytoplasm When it reaches the size of 50 to 60 microns, or more, the nucleus undergoes mitotic divisions A division of the cytoplasm does not begin until about 2,000 nuclei are present During the nuclear division, the sporangium increases in volume, reaching 250 to 300 microns at maturity At this stage, some of the spores become ripe and are arranged

*Editor's note (O F) Rhinosporidiosis of the lacrimal sac is more frequent in India than in the Americas

about the periphery of the sporangium, while the remaining daughter spores, which continu to develop, occupy the center The spores leaving the sporangium are covered with mucilaginous substance, and according to some authors, escape from the sporangium throug an open pore Parodi (1926), however, denied the existence of such an orifice and believe that spores are released by the rupture of the sporangium.

The fact that nuclear division is simultaneous and cytoplasmic division follows late leaving no residual mass around the nuclei, supports the theory that the organism does nc belong to the Protozoa, but due to these characteristics should be placed in Phycomycete Brumpt (1936) considered this parasite as belonging to the family Olpidiaceae of th Phycomycetes

The fungus which causes rhinosporidiosis has not been cultivated It is calle *Rhinosporidium seeberi* (Wernicke) Seeber, 1912 synonyms include *Coccidium seebe* Wernicke 1900, *Rhinosporidium kinealyi* Minchin and Fantham, 1905

LABORATORY DIAGNOSIS

Laboratory diagnosis is limited to microscopic and to histologic exam inations In direct examination mucous exudate is examined between slide in a drop of Lugol solution The mucus is obtained by pressing one of th



Fig 411—Sporangium of *Rhinosporidium seeberi* showing numerous spores.

polypoid masses with forceps It is recommended that material adherent to the forceps be examined Nasal secretion may also be used, although th former mucus is more diagnostic When studied microscopically under lov and high dry powers, the material shows sporangia filled with spores, im mature forms and free spores

In a histologic section, diagnosis is made by observation of the fungous elements of different diameters, corresponding to various stages of development, from small spores, 5 microns in diameter, to mature sporangia, 300 microns, filled with spores

Hematology, Immunology, Culture, and Inoculation of Animals—No studies are known concerning hematologic changes and existence of antibodies Culture has been attempted as well as animal inoculation, but without success

PATHOLOGY

The tissue reaction commonly observed is chronic inflammation with infiltration by plasma and epithelioid cells lymphocytes, as well as by foreign body giant cells Abundant connective tissue causes the growth of the polypoid mass and the formation of capillary vaults After spores have been released from the sporangium an area of necrosis with intense inflammation is seen, with polymorphonuclear, lymphocyte, and plasma cell infiltration

Numerous parasites are seen in various stages of development, beneath the scaly epithelium Large sporangia filled with spores, remnants of empty sporangia immature forms with a central mass surrounded by granular cytoplasm and other stages in which numerous chromatin particles begin to appear, and spores just released from the sporangia are observed

TREATMENT

Initial lesions although superficial, should be carefully extirpated In extensive lesions complete surgical ablation is necessary, with the use of thermocautery to prevent reinfection Medical treatment is only of relative value It may be attempted in the beginning or when the disease is localized in such areas as the eye where surgery is not convenient Allen and Dave (1936) obtained good results by the use of pentavalent antimony (Neostibosan Bayer) accompanied by surgery The antimony is injected intravenously, in doses of 0 30 Gm daily or every other day, until a total dose of 2 to 4 Gm has been given

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CHAPTER 51

SOUTH AMERICAN BLASTOMYCOSIS

FLORIANO PAULO DE ALMEIDA

Synonyms—Brazilian blastomycosis, paracoccidioidal granuloma or granulomatosis Lutz Splendore s and de Almeida s disease Almeida s disease

DEFINITION

South American blastomycosis is a chronic fungus produced condition at first localized preferably in the mouth and the corresponding lymph nodes and gradually invading other lymph glands and lymphoid organs as well as the skin in many cases

GEOGRAPHIC DISTRIBUTION

The first cases of this mycosis were found in São Paulo and were reported by Lutz and Splendore early in this century Other observers have since reported several new cases elsewhere in Brazil particularly in Rio de Janeiro and Minas Geraes For this reason the condition identified as a blastomycosis was given the name "Brazilian blastomycosis After other cases were found in several other South American countries the disease became known as "South American blastomycosis "

It has been reported from Argentina Uruguay, Paraguay, Peru and Venezuela

ETIOLOGY

Lutz maintained constantly, from the very beginning of his observations in São Paulo that the parasite found in his cases was not identical with that found either in coccidioidal granuloma in Argentina and the United States or that found in blastomycosis Splendore (1912) was the first to name the parasite *Zymonema brasiliense* The parasite was later identified as *Coccidioides immitis* by Carini and as *Zymonema histoporocellularis* by Heberfeld (1919) Subsequent investigators following O da Fonseca Filho, adopted Carini's nomenclature

Based on our own researches made since 1926 we have concluded however that the Brazilian fungus is completely different from *Coccidioides immitis*, and in 1929 we named it *Coccidioides brasiliensis* This name we changed to *Paracoccidioides brasiliensis* (1930), and our change has been readily adopted by other investigators especially abroad It is true that Fonseca Filho (1929) attempted to have the name of the fungus changed to *Lutziomyces histoporocellularis*, but this change has not been accepted by other specialists

Moore examined several cultures of this fungus and thought that two new species could be distinguished namely *cerebriformis* and *tenuis* Many mycologists however are inclined not to accept such species as valid, but believe rather that they are variants of *brasiliensis*

Conant and Howell have of late considered *P brasiliensis* as closely allied to the agent of North American blastomycosis which they improperly call *Blastomyces dermatitidis* giving the name *B brasiliensis* to the Brazilian fungus Unfortunately, the genus Blastomyces has neither any mycologic meaning nor is its existence justified

So far *P brasiliensis* has not been isolated in nature from soil plants or animals It has been found only as a parasite of man

INCIDENCE

This form probably exists as a saprophyte particularly on vegetables since the majority of the patients showing buccal lesions are in the habit of chewing plant leaves or using different plant fragments as toothpicks.

Moreover South American blastomycosis affects especially farmers or field workers Our statistics show that out of 875 cases reported from Brazil (March 1947) about 600 are agriculturists or *people engaged in tilling the* soil.

Age—Age seems to have no definite role in the incidence as seen in the following table

AGE		INCIDENCE
Under 10 years	—	21 cases
11 to 20 years	—	117 cases
21 to 30 years	—	165 cases
31 to 40 years	—	162 cases
41 to 50 years	—	1[illegible]3 cases
51 to 60 years	—	105 cases
Over 60 years	—	40 cases
Unknown	—	9 cases

Sex—Of the 875 cases 762 were men 73 women in 40 cases the sex *was not reported*

Nationality—The distribution was Brazilian 447 Japanese 162 Italian 33 Portuguese 36, and Spanish 78 the balance were various other nationals or unreported

In the course of our 20 years of study of mycoses we have been able to find 6[illegible]1 cases of South American blastomycosis registered in the state of Sao Paulo Although I[illegible]alho (1946) states that about 300 cases have been reported elsewhere in Brazil we have found reference to but 64 cases in Rio de *Janeiro* 42 in Minas Geraes and 12 in Rio Grande do Sul Fewer cases are listed as coming from the rest of our territory, 58 having no data

Race—There were 541 whites 162 Orientals 74 Negroes and mulattos

Marital Status—Of 875 cases 420 were married 209 single and 25 were widowed

SYMPTOMATOLOGY

The clinical symptoms are manifold depending upon the localization of the parasite In general the symptoms can be divided into 4 groups (1) *external forms* cutaneous or mucosal of which the mucosal form is by far the more fre

quent and is especially found in the mouth, (2) *lymphatic form*, characterized by lymph swelling generally starting from the neck and affecting the remaining lymph glands (3) *visceral form*, represented by primary lesions occurring in such viscera as the spleen the liver, intestines or lungs, localization of the fungus in the lung has of late been noted much more frequently, so that it is considered virtually a constant finding, (4) *mixed form*, corresponding either to the association or to the succession of the above forms, thus deserving special attention

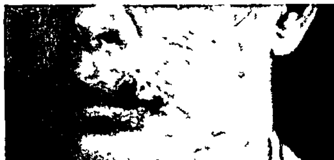


Fig 412 —Mucocutaneous initial lesions of South American blastomycosis (photograph by Almeida and Lacaz) (Courtesy of Antonio González Ochoa.)



Fig 413 —South American blastomycosis Lip lesion (inner side) Case in Dermatologic Clinic of A Pupo São Paulo

External Forms—As we have shown the blastomycosis lesions originate as a rule in the mouth, where they present a rather characteristic aspect The mucous membrane becomes granular and shows reddish spots on a yellow background (berry like stomatitis) These lesions very frequently appear about the gums or the palate, thence extending toward the lips, which become swollen The lesions also customarily reach the surrounding skin, where they assume a variable aspect (ulcerovegetative or papulopustular lesions) and invade the tongue

Since the lesions commonly belong to the most variable types it is essential, before establishing a diagnosis, that the parasite be recovered in



Fig 414 —South American blastomycosis. Close-up. Case in A Pupo's Dermatologic Clinic, São Paulo



Fig 415 —Nasal cutaneous lesions in a case of South American blastomycosis which also presented laryngeal lesions In this case tracheotomy was practiced as shown in the photograph. (Photograph by Almeida and Lacaz) (Courtesy of Antonio González Ochoa.)

material from the affected region There may be 9 different types of external lesions from an anatomic-clinical standpoint, judging from the findings of Aguiar Pupo and Cunha Motta Although the mucosal lesions may be very long in invading the lymph channels, as a rule they are accompanied by local lymph swellings terminating in pus formation and ulceration.

Since the fungus invades the lymphatic system, generalization of the disease is a natural outcome if the patient is not given efficient treatment.



Fig 416—South American blastomycosis Cutaneous ulcero-cutaneous lesions (Photograph by Almeida and Lacaz) (Courtesy of Antonio González Ochoa)

Lymphatic Form—The lymphatic form may occur independently from an apparently primary mouth lesion In some cases the abdominal lymph glands are the first to show swelling and this renders the clinical diagnosis impossible unless one resorts to laboratory tests (intradermal reaction, complement fixation tests, and, if possible, direct examination of the fungus obtained by gland puncture or biopsy following laparotomy).

Visceral Form—A primary visceral lesion must be rare. Viscera most often attacked secondarily are the spleen and the liver, so that the infection may be called hepatosplenoglandular blastomycosis (Dias da Silva and Souza Campos).

Through a recent analysis, the localization of the fungus in the lungs was found to be a very frequent occurrence, and apparently the primary lesion



F g 41 —South An eric n blasto my osis Lung l s ns Case in A. P pe s D n atol gic C nic São Paul o



Fig 418—Radiograpl sl wing pu n onary l sions in a case of S uth Ameri an llaston ycosis (Phot grapl by Alme la an l La az.) (Courtesy of Anton o Gonzá ez Ochoa.)

In the light of modern investigations, our own figures and those of Cunha Motta on lung involvement should be modified, inasmuch as Fialho has just (1946) referred to incidence of pulmonary localization of *P brasiliensis* as 84 per cent in our type of blastomycosis

Mixed Form—In general, this is most frequently seen in old cases since the fungus after lowering the resistance of the host, succeeds in spreading and reaches the lymph glands and internal organs

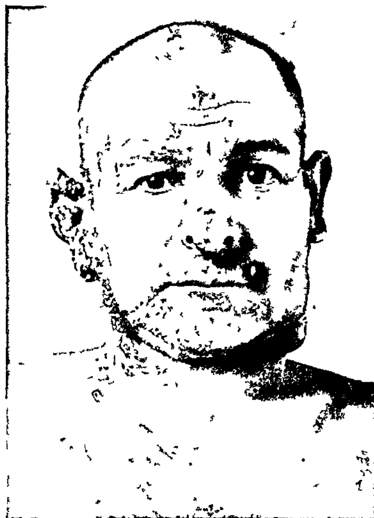


Fig 419—South American blastomycosis Mixed lesions Case in A. Pupo s Dermatologic Clinic, São Paulo

On the whole, it may be stated that the clinical picture in South American blastomycosis parallels the evolutionary stage or the age of the process and this undoubtedly depends upon the patient's resistance In many cases, *P brasiliensis* has been isolated from the blood stream, the infection being hematogenous instead of lymphatic

HISTOPATHOLOGY

Various investigators have described the pathologic lesions found in South American blastomycosis In this regard Cunha Motta has published valuable contributions and Fialho in his thesis for the professorship at the Rio Medical Faculty gave a detailed account of the pulmonary lesions brought about by the fungus

In general the lesions are of a granulomatous type showing at times numerous giant cells with parasites in a more or less advanced stage of phagocytosis Such lesions present slight variations according to their site In the lymph glands for instance Cunha Motta has described 3 forms nodular diffuse and gummatoid which not only express the patient s degree of resistance but sometimes facilitate the diagnosis as well

Different types of lesion have also been registered elsewhere and as a whole they depend on the age of the process From both the macroscopic and the microscopic standpoints the lesions caused by *P brasiliensis* particularly in the lymph glands and the lungs are likely to be confused with those found in tuberculosis in this case only the study of the fungus itself will establish the differential diagnosis

EXPERIMENTAL INOCULATION

Results of experimental inoculations of animals with the fungus are inconstant Guinea pigs are usually the most sensitive laboratory animals particularly when injected by the testicular route and not rarely do the lesions spread beyond the inoculated organ The peritoneal cavity in guinea pigs may also be used as Peryassu (1946) has shown

DIFFERENTIAL DIAGNOSIS

South American blastomycosis must be differentiated from some diseases The lymphatic form might be confused with both lymph gland tuberculosis and Hodgkin s disease The external form may sometimes be mistaken for syphilis leishmaniasis yaws tuberculosis or some neoplasms In these instances the correct diagnosis depends either upon discovery of the fungus microscopically or upon isolation of the parasite in culture media a rather tedious and difficult procedure

In other clinical forms diagnosis is based on finding the parasite in pus secretions or lesions in tissue

MYCOLOGIC DIAGNOSIS

In most cases it is possible to make a diagnosis of South American blastomycosis merely on clinical grounds but it is always advisable to use laboratory methods Laboratory methods applicable thereto are (1) direct examination (2) biopsy (3) cultivation, (4) skin test, (5) complement fixation test, and other tests

Direct Examination—Place a drop of pus or a fragment of some lesion between slide and cover glass and observe under the microscope

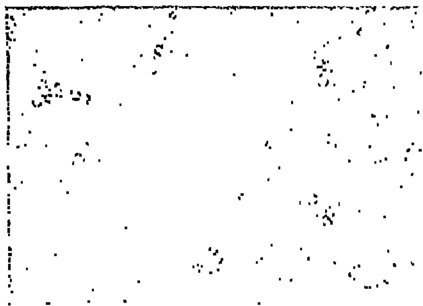


Fig 420—South American blastomycosis *P brasiliensis* in fresh pus (examined between slide and cover glass)

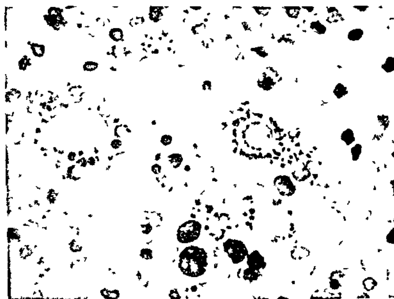


Fig 421—South American blastomycosis *P brasiliensis* in different stages of evolution in lymph gland lesion

For identification, the parasite must show its typical morphology consisting of globose cells of variable size (3 to 4 microns sometimes 10 to 15 or more in diameter) with a thick membrane with a double layer appearance the fungus showing a characteristic multiple sprouting Among these cells the central one or the largest is surrounded by several smaller cells usually globose, elongated or pyriform

In biopsy, or in necropsy, the morphology of the fungus is also very characteristic In the affected tissues *P brasiliensis* shows its typical multiple sprouting and a larger cell surrounded by smaller cells and connected with these at times by an expansion These parasitic forms appear either free or within phagocytes sometimes in very large numbers



Fig 4[illegible] —South American blastomycosis, *P brasiliensis* [illegible] month old culture

P brasiliensis grows in Sabouraud s medium rather sluggishly, usually requiring more than 20 days before growth becomes apparent

Almeida and Fernandes (1944) succeeded in devising a process whereby the fungus grows rather rapidly with visible growth on the fifth day, acquiring a cerebriform appearance This process consists in cultivating infected material (pus or exudate from the lesions) on chocolate agar

and keeping the culture tubes in the incubator as 37° C At room temperature, on solid media the fungus forms whitish furry colonies resembling the skin of white mice When such colonies age, they sometimes appear dried and grooved Under the microscope the cerebriform growths show the parasite with morphology similar to that encountered in tissues, that is, consisting of globose cells with multiple sprouts The furry colonies are thread like and consist of elements called "conidia" of "chlamydospores" At 37° C, the colonies of *P brasiliensis* become cerebriform in appearance, acquiring the furry feature again when they are returned to room temperature It should be remembered that cultures of *P cerebriformis* keep their brain like appearance both at 37° C and at room temperature

Cultivation of the parasite is indispensable to the diagnosis inasmuch as certain yeasts may simulate *P brasiliensis* in the tissues

In addition to these 3 fundamental methods, the following method may also help to establish a diagnosis

Skin and intradermal reactions are now used by Almeida, Silva Lacaz and Cunha (1945) who have prepared 3 different batches of paracoccidioidin They have found this useful as an auxiliary means both for diagnosis and for prognosis The results of this test must, however, be checked by the clinical data In severe and well developed cases, the test is negative and may denote a state of anergy with unfavorable prognosis In a very high percentage of mild cases or in patients with fairly good health conditions, the test is positive The antigen is prepared from old (3 months') cultures in Sabouraud's liquid medium using a large number of different strains (15 to 20)

The filtrate of the culture is injected intracutaneously or intradermally into the forearm in a dosage of 0 1 c c The test is read 24 hours later A positive reaction shows an erythematous or sometimes maculopapular zone, which is usually quite marked and slightly pruritic

Complement fixation test, blood sedimentation rate, and other tests may be valuable when supplemented by clinical data They aid especially in controlling the course of treatment and the cure

TREATMENT

For many years therapeutics was of no avail against South American blastomycosis This disease was considered a true scourge, since the number of cures was both scarce and problematic

With the advent of the sulfonamide drugs, a few encouraging results have been reported It has been found that sulfonamides, through their mycostatic action, aid in the treatment by paralyzing the growth of the fungus, and thus permit the natural defense of the body to prevail in killing the parasite With respect to this, laboratory tests made by Almeida, Silva Lacaz, and Forattini have shown that only sulfadiazine, sulfaglycine, and sulfamerazine have a marked in vitro activity against *P brasiliensis*

In order to stimulate the reaction of the body, we have for many years prepared a polyvalent "vaccine," the effect of which has been very marked in the treatment of numerous patients Based on our experience, we advise

the following method for treatment of this mycosis a sulfonamide drug preferably sulfadiazine or sulfamerazine, sulfathiazole being more toxic 6 to 8 tablets a day for a long time (a few months) Polyvalent antiblastomycotic "vaccine," injection of 1 c c every fourth day in a series of 10 injections and after a short interval a new series of a stronger vaccine It is also recom



Fig 423—South American blastomycosis Same patient as shown in Fig 419 recovery following 8 months of treatment

mended that antitoxic and antiinfectious medication be used especially a rich diet, to aid the resistance of the patient If the treatment is discontinued before it has been completed, relapse of the disease occurs

This method of treatment has resulted particularly in São Paulo in numerous cases of clinical cure of South American blastomycosis See Figs 419 and 423, same patient

PROPHYLAXIS

Since the fungus has not been found as yet in a free state in nature, prophylaxis is purely a personal application Individuals are advised not to chew on leaves or pieces of wood, to keep the mouth clean, and to apply for treatment early when there are any suspicious lesions Such a prophylaxis is very precarious, in view of the wide range of the disease and the depressed cultural state of the people who live in the affected districts, and who seek medical relief only when lesions have become quite widespread

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CHAPTER 52

HISTOPLASMOSIS AND MELIOIDOSIS

R B H Gradwohl

HISTOPLASMOSIS

Histoplasmosis is a disease entity due to infection with one of the fungi imperfecti known as *Histoplasma capsulatum* This infection was first observed by Darling (1906) in Ancon Hospital Panama while looking for kala azar leishmaniasis He found it to be a fatal infection with irregular fever emaciation and enlargement of the spleen and at autopsy showing smears and tissue sections with cells filled with small microorganisms similar to Leishman Donovan bodies They differed however from those seen in kala azar in the arrangement of the nuclei and absence of a blepharoplast He found two other cases and published a second report in 1909 Da Rocha Lima (1912) reviewed Darling s cases and concluded that the *Histoplasma capsulatum* was a fungus Other articles have been contributed by Calli Valerio (1909) Meleney (1925) Ota Masas (1923 1925) and Phelps and Mallory (1926) The next case was reported by Riley and Watson (1926) as originating in Minnesota The next case was reported by Crumrine and Kessel (1931) and originated in California Dodd and Tomkins (1934) reported the first case recognized during the life of the patient the yeast like parasites being found within large mononuclear cells in supravitally stained blood films The cultural characteristics were described by De Monbreun (1934) who isolated the organisms from the spleen De Monbreun (1939) reported a case where the dog was considered as a natural host for this parasite Moore (1934 1935) studied these organisms and concluded they should be classified as belonging to the genus Posadasia family Coccidioideacea and species *capsulatum* Ramsey and Appelbaum (1942) reported another case in a woman who had lived in Michigan all her life never having visited or lived in the tropics This patient had a continuous fever and finally died after lapsing into coma Autopsy revealed an interstitial pneumonitis with thickening of the alveolar walls and a definite increase in connective tissue around the smaller bronchioles and blood vessels and a reticuloendotheliosis There were numerous large endothelial macrophages lining the alveolar spaces and in the alveoli These were filled with the organisms The spleen showed interstitial fibrosis All of the sinusoids contained numerous endothelial macrophages filled with the organisms and numerous parasites were free in the tissues The lymph nodes were extensively involved and showed the microorganisms Bone marrow sections showed many organisms in the large phagocytic cells

The following further details of this fungous infection were submitted to us by Arden Howell Jr Instructor of Tropical Medicine Tulane University of Louisiana New Orleans La

EPIDEMIOLOGY

Prevalence —

GEOGRAPHIC DISTRIBUTION OF KNOWN CASES

United States	32
Hondurıs	1
Panama	3
Brazil	2
Argentina	1
Philippine Islands	2
Jarı	1
Total	42

INCIDENCE OF CASES BY YEARS

1906	2
1908	2
1926	3
1931 1934	4
1939 1941	31
Total	42

DISTRIBUTION OF CASES IN THE UNITED STATES

California	2	Indiana	2
Tennessee	5	Florida	1
Iowa	1	Texas	1
Missouri	2	Mississippi	1
Michigan	5	Minnesota	1
Virginia	2	Maryland	2
Kentucky	1	Alabama	2
Illinois	1	Washington D C	1
Ohio	2		

Reservoir —Dogs and prol al ly some ro lents
Transmission —Unknown

PATHOLOGY

The parasites are found within the reticuloendothelial cells Any, all, or a combination of the following organs may be involved

Skin —Multiple lesions primarily in the corium with secondary papule formation and eventual ulceration

Nasal or Oral Mucosa —Single or multiple granulomatous lesions in the submucosa with the formation of patches and early ulceration

Lymph Nodes —Lesions resemble tuberculosis

Lungs —Lesions multiple, varying from microscopic infiltrations to nodules necrotic areas, abscess cavities, or both

Intestine —Lesions vary from nodules to ulcers, the latter pin point in size to large, macroscopic granulomatous areas

Liver and Spleen —Inflammatory foci scattered throughout, miliary nodules with or without caseation, in advanced cases, necrosis of the parenchyma Usually splenomegaly and enlarged liver due to proliferation of connective and reticuloendothelial tissues eventually cirrhosis of the liver

Adrenals —*Foci in cortex and medulla, with eventual caseation*

Bone Marrow —In generalized infections almost invariably involved

Blood —In septicemic infections the number of both red and white cells is decreased

DIAGNOSIS

The symptoms suggestive of histoplasmosis are ulcers of the skin, nasal or oral mucosa, enlarged lymph nodes, obscure lung infection, intestinal ulcers, enlargement of liver, spleen, or both, anemia, leucopenia, irregular fever

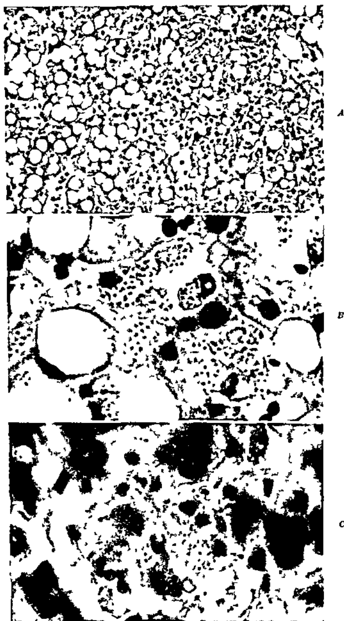


Fig 424—Human liver *A* *Histoplasma capsulatum* low power *B* *H* *capsulatum*, oil immersion *C*, kala azar for comparison. (Courtesy of Oscar Felsenfeld.)

The diagnosis must be confirmed by demonstration and identification of the organism In tissue *Histoplasma capsulatum* resembles *Leishmania donovani* The differentiation is based on the presence of a capsule and the absence of a blepharoplast in Histoplasma

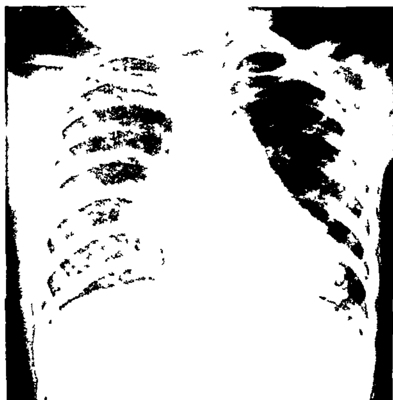


Fig 425 —X ray of chest of child with histoplasmosis (Courtesy of H S Gordon Assistant Superintendent Children's Hospital of Cook County Chicago and Oscar Felsenfeld)

MATERIAL TO BE EXAMINED

In Localized Infections —Scrapings biopsies aspirated material

In Generalized Infections —*Early*, puncture of the sternum or spleen, *late*, peripheral blood

Technic of Examination

Scrapings from lesions and smears from bone marrow or blood should be stained by the Giemsa method and examined with an oil immersion objective for the presence of encapsulated yeast like organisms within the reticulo endothelial cells Biopsies should be rapidly sectioned and are best stained by the Giemsa method

To isolate the fungus infected material is cultured on Sabouraud's media beef infusion broth and agar, and blood agar, at 22° and 37° C Growth may not be apparent before 3 or 4 weeks

TREATMENT

Results of treatment have been very discouraging It some cases to resort to surgery Some authorities have of antimony compounds—antimony tartrate and Fuadin of very little value when the disease has become generalized

MELIOIDOSIS

In synonyms of this disease are Stanton s disease and *mallei* It occurs in Burma the Malaya States and Ceyl resemblances to tularemia because both are diseases of r dentally attack man It closely resembles glanders I Stanton and Fletcher in 1932 although earlier Whitmore bacterium in autopsies of babies in Rangoon Krishnaswa in Rangoon Other cases have been reported in Singapore

The *Bacterium whitmori* closely resembles *M mallei* and occurs in very large numbers in all acute lesions of Leishman s stain bipolar staining is commonly seen It res bacillus in colonies but is more actively motile

The first case reported in the Western Hemisphere is th Varney (1947) In their case a white man showed ulcers right buttock and thigh of 8 years duration His medica beginning of this pathology in a fall with injury of the co was followed by dark swelling and appearances of infectio on he had many episodes including formation of abscesses

The specific organism was recovered repeatedly from of pus and tissue debris Cultures of the patient s blood negative The organisms from both the smooth and rough c staining bipolar gram negative and nonacid fast and ur tions they exhibited rapid serpentine mobility This is description in most textbooks namely a more rapid motion Those from rough colonies averaged 2 by 0 6 microns in siz smooth colonies were usually longer and narrower occ a length of 5 to 6 microns They showed parallelism an ranged in an irregular network The bacilli appeared enca in freshly isolated cultures or animal lesions but no cap strated by staining The colonies exactly resembled th *mallei* as described by Topley Growth was strictly aerob grew rapidly and profusely on all commonly used media a velopment being especially good on media with a tryptose blood agar than on plain agar Colonies of the smooth form and mucoid and often grew to a diameter of 8 mm These co grayish white but changed to a deep brown They were surr

The diagnosis of melioidosis was carried out by bacteriologic investigations for the purpose of differentiating it from the glanders bacillus McDowell and Varney's experiences are typical of the bacteriologic methods to be employed.

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CHAPTER 53

ARTHROPODS—DIRECT AGENTS IN TROPICAL DISEASES

LUIS VARGAS

Arthropods are bilaterally symmetrical metazoa with a chitinous exoskeleton segmented body and articulated legs In some a nascent state of parasitism can be observed since they may be found as predaceous or parasitic or saprozoic organisms for example *Pediculoides ventricosus* The parasitic state not only affects the host but results in a sort of mutual adaptation the perfect parasite causing a minimum amount of damage and the host reacting almost imperceptibly The adaptation may require morphologic and functional modifications in the host as well as in the parasite

Arthropods may be *facultative* parasites that is they may be capable of living not only as parasites but they are able also to live apart from the host or they may be *obligatory* parasites incapable of living apart from the host and therefore living in or on the host for all or a part of their existence

Obligatory parasites such as *Pediculus humanus* die when removed from their host Mosquitoes are *intermittent parasites* while *Sarcoptes scabiei* the parasite which causes itch never leaves the host Some are parasites exclusively of man while others parasitize both man and lower animals There is *accidental parasitism* for example those myriapods which may live for days or for months in the human body but which are only rarely encountered in man The name *periodic* parasite is given to that type of parasite which passes the early stages of its development within or upon a host as in the case of myiasis

In some arthropods such as mosquitoes sand flies gnats and horseflies only the female sucks blood this being the basis of its nutrition or stimulus for the formation of the eggs In other types bedbugs fleas and ticks the males as well as the females bite In the *Auchmeromyia luteola* only the larvae suck blood

No clear line of separation can be indicated between external and internal parasites some very small ticks larvae of flies pentatomes *(Linguatula)* etc may be considered as belonging to either of the two groups

Entomophobia is abnormal fear of insects it appears in certain mental states in neurotic individuals or in otherwise normal persons after a psychic shock

Independent of their role as vectors arthropods may cause disease by various mechanisms

1 **Debilitation**—They may be responsible for the so-called secondary anemias due in part to loss of blood and in part to some toxic substance which acts upon the hematopoietic organs

2 **Mechanical Irritation**—The pathologic picture may be due to an arthropod or to a part of one and may be aggravated by a toxic secretion Frequently accidental or erratic parasitism is involved in this instance

3 **Poisoning**—Introduction of the saliva of the insect may provoke reactions which may be mild or grave, frequently with allergic manifestations similar to those caused by histamine and poison effect The venom frequently is very complex and produces various effects the most important being the vasodilatory and hemorrhagic effects allergizing cytolytic, coagulant neurotoxic vesicant thermogenic and pruriginous The poison may be introduced by a bite or a sting as in the case of the South American ant known as tucandeira *(Paraponera clavata)* or fire ant of California and Mexico *(Solenopsis xyloni var maniosa)*, or the harvest ants of Texas and California (*Pogonomyrmex barbatus* and *Pogonomyrmex californicus*, respectively) The so called centipedes of the classes Chilopoda and Diplopoda and spiders also are included in this group as well as aquatic Hemiptera of the families Belostomidae and Notonectidae Poisoning due to introduction of the sting is observed in the case of the honey bee or of the wasp such as *Vespula diabolica*, family Vespidae order Hymenoptera commonly called yellow jackets or hornets Scorpions also belong in this group In the group which causes intoxication by means of nettle like hairs are included larvae of butterflies or caterpillars order Lepidoptera with species included in the families Megalopygidae Eucleidae Thaumetopoeidae Limantriidae Arctiidae Noctuidae Saturniidae and Nymphalidae*

Vesicant fluid is produced especially by species of the order Coleoptera Beetles accidentally swatted on the skin produce a vesicular dermatitis through a volatile substance called "cantharidin" Some species of Paederus family Staphylinidae called "pichuyes" or rove beetles contain a substance similar to cantharidin but which differs in that the effect appears 1 or 2 days after contact the best known species are *P amazonicus* and *P columbinus* of Brazil and *P irritans* of Ecuador Under the name of seasonal vesicular dermatitis or temporary phlyctenular dermatitis there has been described in Guatemala a disease produced by Staphylinidae The disease appeared during the month of April and affected many of the laborers who had been working at night

A fluid extracted from *Diamphidia simplex*, family Chrysomelidae is used by the Bushmen in South Africa to poison their arrows Species of the families Oedemeridae and Paussidae also are mentioned as producing vesicular dermatitis *Tribolium confusum* emits a gaseous substance which is irritating to the eyes and nasal mucosa Some of the Phasmidae order Orthoptera commonly called "campamochas" walking sticks stick bugs throw off a fetid fluid which occasionally has been known to injure a person's eye

In the group of diseases caused by arthropods and which are classed as infestations are included myiasis canthariasis scoleciasis itch and tungiasis

*In French Guiana a pruriginous dermatosis has been described caused by the stinging hairs of the female butterfly of the genus Hylesia family Saturniidae

CHAPTER 54

MYIASIS

LUIS VARGAS

DEFINITION AND RELATED TERMINOLOGY

Myiasis is a term used to designate a pathologic state in man or animals caused by diptera themselves in various stages of development. The term commonly used only in connection with the larvae of flies was first introduced by Hope (1840) and originally referred only to the larvae of Diptera which cause disease. This author also formulated the term "canthariasis" for the morbid state in which the larvae of Coleoptera are the etiologic agents. Canthariasis always intestinal may be due to *Tenebrio molitor* of Linnaeus a tenebrionid of the family *Tenebrionidae*, or to *Blaps mortisaga* of Linnaeus a tenebrionid of the subfamily Blaptinae or it may be due to *Calandra oryzae* a curculionid. All of these are very widely distributed and are accidentally ingested with cereals flour etc.

The term "scoleciasis" was considered at first for cases due to Lepidoptera. Porocephaliasis implies infection of the human being by porocephalids of the class Arachnida order Pentastomida family Linguatulidae. These aberrant animals with a very complicated life cycle may be found in the valleys of the frontiers of Europe. *Armillifer armillatus* (Wyman 1847) is relatively common in certain parts of West Africa especially in the Belgian Congo where it is found in the respiratory system. *Armillifer moniliformis* (Diesing 1836) is found from Africa to the Philippines and Australia. The pathology is similar to that of the preceding species.

LIFE HABITS

Myiasis is divided into cutaneous, intestinal, nasal, ocular, auricular, urinary and vaginal according to localization. Various types of this affection have been described from the most remote periods of the past, references to it are found in religious books, literary works and historical accounts. In the New World it has been known since 1587 when Soares de Souza first described cases of cutaneous myiasis.

Myiases are generally observed in the warmer seasons of the year. They are more frequent in children than in adults. Usually infected are persons who live outdoors in the fields in contact with animals and who are careless in their hygienic habits. Some forms of myiasis pass unnoticed through the host the parasite being found accidentally. Intestinal myiases are especially of this type and for this reason it is difficult to state their true incidence. Parasitism by flies may be due to specific, semispecific or accidental tropism

of the insect In the last two circumstances the larvae or pupae develop in decomposing organic material such as food excrement wounds etc and entrance into the body easily occurs With many species of insects this accident may be fatal

Many species have been found in the digestive canal of man and in fecal material but such cases cannot be called parasitism Species so found are included in Drosophila Calobata Piophila Tachina Hydrotaea Musca Pyrellia Philaematomyia Anastrepha and other genera Sometimes myiasis has been attributed to Diptera that regularly or accidentally are found in fecal material but which have not actually been expelled by the supposed host

According to Salem (1935) Desoil and Delhaye in 1922 in experimental investigations with eggs of *Calliphora vomitoria,* found that human gastric juice does not prevent the hatching of larvae from eggs which have been in the juice for 3 to 8 hours at 37° C if however the eggs remain in the juice for 10 hours the larvae do not develop Five per cent hydrochloric acid has no effect on the eggs in 2 to 5 hours After a lapse of 2 to 7 hours at 37° C in 2 to 10 per cent solutions of hydrochloric acid the larvae were observed to emerge from the eggs These authors concluded that the eggs pass through the stomach without being affected during the digestion of food The resistance of the larvae is quite variable Small young larvae are more vulnerable In organic liquids such as urine feces and bile of dogs the larvae which are merely moistened develop normally at 15° C and with difficulty at 37° C In gastric juice resistance varies from 2 to 5 hours at 37° C for larvae that are submerged in the liquid and from 5 to 12 hours for larvae which are only moistened

From this one may conclude that larvae with intact cuticle apparently are capable of resisting chemical action in the stomach thus making infestation by digestion possible Larvae of *C vomitoria* are very sensitive to lack of air to mechanical obstruction of the stigmas and to pressure for this reason myiasis produced by these larvae is possible only in cases of marked gastrointestinal disturbances with aerophagy In 1924 Desoil (according to Salem 1935) concluded that at least in vitro the eggs of *C vomitoria* are capable of resisting the chemical action of the gastric juice for the period of the normal digestion Observations in vivo show that other factors which are fatal to the larvae may intervene

Causey (1938) found that when larvae of *Drosophila melanogaster Lucilia sericata Phormia regina Cochliomyia macellaria Sarcophaga securifera* and *Calliphora erythrocephala* are fed to dogs and cats the larvae die or become immobilized in the stomach before 3 hours have elapsed and they are eventually digested upon passing into the intestinal tract In no case were living larvae of this species found in the large intestine or in stools of the experimental animals According to this author it is therefore difficult to understand how the larvae can produce the symptoms attributed to them

Riley (1939) discussed experiments carried out by Causey (1938) and believes that while undoubtedly many cases may be justly attributed to con

tamination there are other cases which cannot so easily be dismissed He cites a case in which living larvae continued to be expelled for a long period by a patient who was under strict surveillance In response to the physician's questions concerning the possibility of extracorporeal contamination no such possibility appeared while obtaining samples for study which included material from feces vomitus and from the rectum by proctoscopy Riley (1939) saw several cases in which he was sure that living larvae especially of Sarcophaga and also of Fannia and Eristalis were expelled from human intestines

Mills and Peffer (1939) reported that larvae pupae molts eggs and excrement of *Tribolium confusum* Duval boiled in oatmeal and fed experimentally to humans caused no digestive upsets

The larvae of *Auchmeromyia luteola* or "Congo floor maggot" is an exception among myiasis producing larvae in that it is a blood sucker Sometimes the number of parasites obtained in a clinical case reaches large numbers as in the work of Arreaga (1941) who succeeded in extracting around 200 larvae of *C hominivorax* from the nostrils

Myiasis of the external male genitalia is infrequent In the female cases of vulvar myiasis are more often seen Joseph in 1885 found vulvar myiasis in a child the first case of this type published in Europe In Argentina Barabino Amadeo and Lauregui (1914) presented a case of penile myiasis in a 30 year old patient with about 100 larvae of *C hominivorax* present

There are reported 5 cases of gastrointestinal and 1 case of nasal scoleciasis Hinman and Faust (1932) reported a case in which the larva of *Tenebrio molitor* (Coleoptera) was found in a tonsil In Spain there was found in the inner ear of a patient *Acinopus picipes* subfamily Harpalinae family Carabidae order Coleoptera In the outer ear there have been found "tijeretas" or earwigs (*Forficula auricularia* Linnaeus order Dermaptera) cockroaches and fleas

Control

Satisfactory hygienic conditions reduce the chances of infection Recommendations for betterment of hygienic conditions are necessary The use of repellents such as 6 2 2 sleeping in a tent when camping out and exercise of care in eating clean food are also recommended Animals which have been treated with phenothiazine for helminthiasis produce exereta in which larvae of flies do not develop DDT is very useful in treating manure in direct application to the hides of animals in treating walls of stables dunghills etc

Steward and Boyd (1934) reported that a spray composed of 15 per cent chloroform in almost any light vegetable oil is very useful for exterminating larvae which produce traumatic dermal myiasis

Anesthesia of the larvae appears to be necessary before they can be extracted from cavities etc when living as parasites It is also reported that powdered garlic given by mouth causes their elimination

Dermatobia Hominis (Linnaeus, 1781)

This species is found in the Neotropical regions, in lowland zones around the Gulf of Mexico, Caribbean, and Atlantic regions, from Mexico to Northern Argentina In Spanish it is called the "gusano de monte" In Mexico and Central America it is known by the Aztec name "colmoyote" or "moyocuil", in Venezuela as "torcel", in British Guiana as "anal coshol", in French Guiana as "ver macaque", in Brazil as "berme," "oura," or "ura", and in Peru as *sututo-gusano ' worm or "chute-subj acuro "*

Dunn (1934) referred to a fatal case of myiasis of the brain *Dermatobia hominis* has the interesting habit of utilizing other arthropods for transporting its eggs A great variety of vectors is chosen by the female *D hominis* to carry her eggs This lack of discrimination in choosing vestors results in a great variety of hosts and in a great quantity of larvae which cannot complete their life cycles due to being carried on non blood sucking arthropods The glued eggs found on a vector generally do not exceed 40 in number, but, as 1 female lays from 380 to 400 eggs it is probable that she attacks many individuals of different species *D hominis* parasitizes not only man but also cattle, sheep, dogs, cats rabbits squirrels monkeys agoutis etc

TREATMENT

Treatment varies according to each clinical case To extract larvae from the skin, wounds or cavities minor surgical intervention is sometimes neces sary To withdraw larvae from the skin an application of raw meat or of crushed tobacco compress over the spot is recommended The larvae are generally drawn out easily and painlessly within 24 hours *

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*Editor s note (O F) An alternative method is to freeze with methyl or ethyl chloride the superficially situated larvae and remove them surgically Deeper lying larvae are left until they come to the surface spontaneously Cattle are dipped in 2 5 per cent Rotenone in soap water emulsion

CHAPTER 55

DISEASES CAUSED BY TICKS, MITES, CENTIPEDES, AND LICE

LUIS VARGAS

Order Acarina

This order includes both ticks and mites. They differ from other arachnids and from true insects by lack of body segmentation. In most of them the body is more or less oval with the thorax and abdomen fused in such manner that no line of demarcation is observable between them; others have some tiny mark of separation between thorax and abdomen, and finally the hair follicle mites, *Demodex*, look more or less like worms. The head is incomplete although in ticks the capitulum is considered as a *false head*. As in other arachnids the adults have 4 pairs of legs and the larvae of most have only 3 pairs.

Acarids are widely distributed throughout the world from tropical zones to the poles. Some are free living subsisting on decomposing substances, vegetation, etc.; others are predatory and feed on small animals; some are aquatic; a great many are parasitic. Among them various grades of parasitism are found: some are entirely parasitic while others parasitize only in one stage of their existence; some are intermittent parasites. Moreover, they are important in the transmission of various pathogenic agents, such as viruses, spirochetes, rickettsiae, Salmonellae, Bartonellae, Pasteurellae, Sporozoa, hemogregarines, flagellates, and even filariae.

They may be divided into the following superfamilies: Ixodoidea, in which are included the ticks; Parasitoidea, Eupodoidea, Thrombidoidea, Hydrachnoidea, Tarsonemoidea, Tyroglyphoidea, Sarcoptoidea, and Demodicoidea, which includes mites.

Acarids of importance to medicine are not found in all these superfamilies; we shall concern ourselves only with families of interest in this respect.

Superfamily IXODOIDEA Banks, 1894

Representatives of this superfamily belong to the suborder Metastigmata. They have various common names in different parts of the world; some of them are garrapatas, carrapatos, "ticks," "Zecken," "tiques," etc. They are widely distributed but abound principally in tropical and subtropical regions. They localize principally in those parts of the body where the skin is thin and where there are many blood vessels (abdomen, neck, ears, groin, etc.).

Ixodoidea are differentiated from other acarids principally by the presence of a pair of stigmal plates situated laterally, generally posterior to the fourth pair of feet. They have a false head or capitulum showing several characteristic

structures as follows primarily a basal portion or *basis capituli*, a pair of *palpi*, a pair of *chelicerae* with serrate fingers on the outer edge and a rigid *hypostome*, almost always dentate on the ventral surface

Ixodoidea are divided into 2 families Argasidae and Ixodidae

By using the following key, the genera of these 2 families may be determined

Family Argasidae Canestrini, 1890

(Key from Cooley and Kohls, 1944)

1 With a definite sutural line separating dorsal and ventral surfaces ... *Argas*
Without a definite sutural line separating dorsal and ventral surfaces ... 2

2 Nymphs with integument provided with spines, hypostome well developed; adults with granular integument and vestigial hypostome ... *Otobius*
Integument of adults and nymphs similar in general mammillated or tuberculated without spines hypostome of different forms in nymph and adults but not vestigial 3

3 Hypostome wide at the base and spoon shaped (associated with bats) ... *Antricola*
Hypostome of various forms never spoon shaped (associated with several classes of animals including bats) ... *Ornithodoros*

Family Ixodidae Murray, 1877

1 Without eyes ... 2
With eyes ... 4

2 Mouth parts elongated second joint of pedipalpus longer than wide ... 3
Mouth parts shortened, second joint of pedipalpus slightly longer than wide, scutum not ornate, second joint of pedipalpus extending laterally *Haemaphysalis*

3 Anal grooves anterior to anus, scutum inornate ... *Ixodes*
Anal grooves posterior to anus scutum ornate ... *Aponomma*

4 Mouth parts much larger than basis capituli ... 5
Mouth parts approximately the size of basis capituli ... 6

5 Scutum generally inornate eyes submarginal, ventral plates present in male ... *Hyalomma*
Scutum generally ornate, eyes marginal, ventral plates lacking in male ... *Amblyomma*

6 Fourth coxa larger than the others ... 7
Fourth coxa approximately of same size as others ... 9

7 Spur of fourth coxa very large basis capituli hexagonal, scutum inornate, without adanal plates festoons ... *Rhipicentor*
Spur of fourth coxa small or absent, basis capituli rectangular ... 8

8 Scutum ornate ... *Dermacentor*
Scutum inornate ... *Otocentor*

9 Festoons articulation of fourth pair of legs normal ventral plates present, scutum ornate ... *Rhipicephalus*
Without festoons ... 10

10 Joints of fourth pair of legs normal palpus with transverse border first coxa bifurcated ... *Boophilus*
Joints of fourth pair of legs widened palpus without transverse border, first coxa not bifurcated ... *Margaropus*

Most argasids, like many insects, suck blood rapidly, and are intermittent parasites Ixodids on the other hand, generally attach themselves to the host and remain there for several days or even weeks depending upon certain factors of development Some argasids also remain attached to the host for a long period as in the case of nymphs of *Otobius megnini* just as there are ixodids, such as *Haemaphysalis inermis*, which have a very short feeding period

The number of molts in ticks is variable argasids may have from 3 to 7 or more while the ixodids have only 2 In the first molt they pass from the larval to the nymph stage and in the second from the nymph to the adult state

Fecundity of ticks as well as their life span is of great importance in their role as transmitters of disease In general they produce a fantastic number of eggs As to their life span, it is truly astonishing a tick can survive without food for long periods of time—an argasid can survive for several years without feeding Mating in argasids may be repeated several times taking place in hiding never upon the host They hide within cracks and crevices of houses or in the nests of their hosts and emerge at night to suck blood for a short period of time Larvae and nymphs generally feed several times before molting the adult female generally feeds several times depositing a small pile of eggs after each feeding In some the body is flat and does not increase in size by alimentation for the dilatation due to intake of blood takes place in a dorsoventral direction Larvae and nymphs of Ixodidae feed once during each stage of development

Family **ARGASIDAE** Canestrini 1890

Genus **Argas** Latreille 1796

Argas persicus (Oken) 1818 —This species is cosmopolitan having as hosts principally chickens a great number of which are killed through general exhaustion and as the direct consequences of the bites In Persia it is reputed to be very dangerous even killing people Experimentally the virus of yellow fever has been retained in the tissues of this tick It transmits by development and transovarially relapsing fever in Europe Asia Africa and North and South America

Argas reflexus (Fabricius) 1794 —This species has been observed in England France Germany Italy Russia Romania Algiers Colombia and the United States When these parasites are very numerous they may cause death of pigeons and other birds In man the zone of the bite which is very painful becomes swollen and presents intense pruritus which sometimes extends well beyond the bitten area severe erythematous eruption or urticaria and edema may occur Following the bite there often is nausea vomiting diarrhea dyspnea irregular pulse etc Pyogenic bacteria may be transmitted through the bite giving rise to furuncles abscesses phlegmons etc

Argas mianensis (Brumpt) 1921 —This species is thought to transmit Mianah fever a form of relapsing fever in Iran which is probably transmitted to man through development and transovarially

Genus **Otobius** Banks 1912

Otobius megnini Duges 1884 —This tick is very common in Mexico and has also been reported in the United States [illegible]
Africa and India [illegible]
livestock or horses
it may cause death of cattle

Genus *Ornithodorus* Koch, 1844

Ornithodorus savignyi Audouin, 1826.—In Europe, it transmits the spirochetes of relapsing fever to rodents. Transmission takes place by development and heredity. In Central Africa it transmits to rats and mice the *Borrelia duttoni* of relapsing fever. In North Africa and in the Mediterranean regions it transmits to rodents *Borrelia hispanica* and *B. normandi*. Experimentally it has also transmitted *B. venezuelensis*. This tick has been experimentally infected with the *Trypanosoma cruzi*, which develops within it.

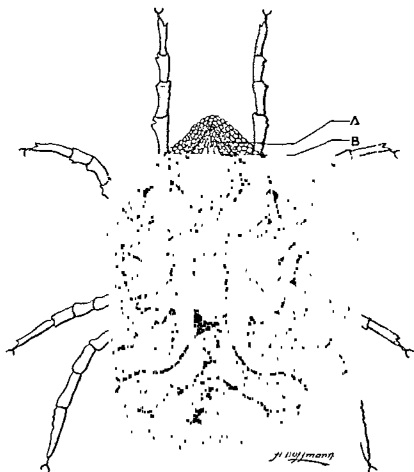


Fig 426.—Ventral view of *Ornithodoros coriaceus* Koch. *A*, mouth parts; *B*, camerostoma; *C*, eyes; *D*, genital orifice; *E*, anus

Ornithodorus moubata Murray, 1877.—This species has produced serious *local lesions in man and animals*. *Its painful bite quickly becomes circumscribed* by a circle of ecchymosis a centimeter in diameter. When attached to man in great numbers, this species may cause anemia. The virus of spring and summer encephalomyelitis has been transported in this tick. It has served as an experimental vector of the yellow fever virus. Rickettsiae of tick fever of South Africa have been transported to the United States in this tick. Transmission of

Rickettsia diaporica has been demonstrated stage by stage and by heredity In Central Africa it can transmit to rats mice and man by development and heredity *Borrelia duttoni* of relapsing fever Experimentally it has transmitted *Borrelia recurrentis* of Russia as well as *B novyi* of America It has transmitted through its bite *P persica* the pathogenic agent of spirochetosis of Central Asia Experimentally it has transmitted *Pasteurella tularensis* but the infection is fatal to the tick It permits development of *Trypanosoma cruzi*

Ornithodorus coriaceus Koch 1844 —A species found in California and Mexico The bite is unpleasant painful and irritating The acute pain is rapidly followed by extensive swelling with numbness at the site The wound may persist for several months forming a scab with lymph exudate

Ornithodorus hermsi Wheeler Herms and Meyers 1935 —Found in the western part of the United States in California Colorado northern Idaho and also in Oregon Washington Nevada and probably in southern British Columbia It transmits by development and heredity the spirochetes of relapsing fever (*Borrelia turicata*)

Ornithodorus nicollei Mooser 1932 —Mexican species By means of this tick rickettsiae of spotted fever of the United States have been transmitted experimentally as well as São Paulo and Colombian typhus It can perhaps be considered as a potential vector in Mexico Hereditary transmission has been demonstrated in the tick *Rickettsia diaporica* may be preserved in the tissues of the tick for more than 200 days but no microorganism is transmitted through its feeding The same is true of *Pasteurella tularensis* This organism is more noxious to the tick since it delays the molting and shortly after the tick has become infected it is dwarfed Experimentaly it can transmit Turkestan relapsing fever

Ornithodorus turicata Duges 1876 —A New World species The bite of this tick is very painful causing extensive swelling and irritation which may in man have serious consequences In some animals for example in hogs the bite is fatal Rickettsiae of Rocky Mountain fever have been found in it but whether the tick transmits the disease is not known Rickettsiae of Q fever have also been found Experimentally the organisms of São Paulo typhus remain actively in its body but are not transmitted through its bite By development and heredity it transmits borrelias of relapsing fever of the United States or *Borrelia turicata* which is found also in Aguascalientes Mexico It also transmits *P venezuelensis* which is thought to be the cause of spirochetosis in Colombia Experimentally it has transmitted *B duttoni B persica* and *B babylonensis* It may carry in its tissues the bacteria of tularemia but it is not known to be the transmitter experimentally it may ingest microfilariae of *Onchocerca volvulus* of man

Ornithodorus parkeri Cooley 1936 —Rickettsiae of United States Rocky Mountain spotted fever have been found in this tick however there is no certainty that it is the natural transmitter It is a very efficient experimental vector of American spotted fever It has readily transmitted experimentally various types of spotted fevers by its bite It can carry *Rickettsia diaporica* in its

tissues the microorganism retaining its virulence for several months, however, infection does not take place during feeding On the other hand, its excreta are infectious By development, it transmits spirochetes of relapsing fever in the northwestern part of the United States It can carry *Pasteurella tularensis*, which retains its virulence for several months, but it is not known to be a transmitter although its fecal matter is infectious Experimentally it is capable of infection by *Trypanosoma cruzi*

Ornithodorus talaje Guérin Meneville, 1849—The bite is very irritating and painful to man and the local effects uncomfortable It transmits *Borrelia venezuelensis*, the cause of relapsing fever of South and Central America principally the hilly parts of South America Guatemala Colombia Panama and Mexico Transmission is effected among the ticks by development and heredity Man rats monkeys and, in general a variety of domestic and wild animals are infected by this species Borrelias of relapsing fever have been isolated from ticks captured in Arizona and Texas, in the United States The species can maintain, for long periods of time, the *Borrelia persica* but cannot transmit it by bite

Ornithodorus amblus Chamberlin, 1920—Found in the Guano Islands of Peru It attacks man, causing lesions which may persist for a long period It has been infected experimentally with *Trypanosoma cruzi*

Ornithodorus rudis Karsch, 1880—Central and South American species *The bite is very painful and produces ecchymosis The species has been* utilized as a medium for transporting rickettsiae of petechial fever of Tobia, Colombia In tropical America it is the most important transmitting agent of the spirochetes of relapsing fever of man, *Borrelia venezuelensis* which it transmits by heredity and development

Ornithodorus capensis Neumann 1901—Cape Province Bite is very painful to man

Ornithodorus pavimentosus Neumann, 1901—The bite of this African species is very painful to man

Ornithodorus erraticus Lucas, 1849—A species from Algeria The bite of this tick is very painful It causes ecchymosis with a diameter of 2 cm in some cases with a passing febrile reaction In North and West Africa, it transmits the *Borrelia duttoni*, the cause of relapsing fever It also transmits to man the *B hispanica* which causes relapsing fever in North Africa and the Mediterranean countries principally Spain Transmission in ticks takes place by development and heredity It may transmit *B persica* by bite

Ornithodorus tholozani Laboulbéne and Megnin, 1882—In Asia Minor and Central Asia this species of tick transmits by development and heredity, *Borrelia persica*, which causes relapsing fever in these regions Transmission is effected by a bite, as is that of *B recurrentis* and *B hispanica*

Ornithodorus lahorensis Neumann, 1908—The bite of this species of Asia Minor is quite painful and troublesome It frequently causes anemia in sheep Experimentally the tick has retained in its tissues *Rickettsia prowazeki* for 25 days at the expiration of which time it was capable of transmitting the infec

tion Through development and heredity it transmits borrelias of relapsing fever in Asia *Trypanosoma cruzi* can develop and multiply in the body of this tick

Ornithodorus furcosus Neumann 1908 —Ecuador This species has been experimentally infected with *Trypanosoma cruzi*

Ornithodorus rostratus Beaurepaire Aragao 1911 —This species is found in Brazil The bite produces in man extensive areas of ecchymosis The injected anticoagulant produces prolonged hemorrhage It is capable of causing ulcers It may transmit experimentally by bite the virus of yellow fever transmission to certain primates has been effected It has transmitted experimentally rickettsiae of São Paulo typhus

Ornithodorus braziliensis Beaurepaire Aragao 1925 —In Brazil The bite produces local and general reactions in man with erythemas and pruriginous papules at the site of the bite followed by headache and fever

Ornithodorus normandi Larrousse 1923 —In Tunis The bite is but slightly painful causing only slight pruritus and ecchymosis It transmits *Borrelia hispanica* the cause of relapsing fever of North Africa and the Mediterranean

Ornithodorus foleyi Parrot 1928 —In Algiers The local lesion produced by the bite resembles a furuncle or a syphilitic chancre provokes fever

Ornithodorus verrucosus Olenev Sassuchin and Fenink 1934 —In Asia Minor and Central Asia It transmits both by development and by heredity *Borrelia persica* the cause of relapsing fever in these regions

Ornithodorus asperus Warburton 1918 —In the Near East It transmits *Spirochaeta babylonensis* in the Mediterranean regions in the Bileel Steppes to the east of Iran

Ornithodorus tartakovsky Olenev 1931 —It transmits spirochetes of relapsing fever in the desert steppes of Central Asia and Turkmenistan

Ornithodorus gurneyi Warburton 1926 —In Australia Through the bite it can produce generalized paralysis blindness and loss of consciousness

Family **IXODIDAE** Murray 1877

Genus **Ixodes** Latreille 1795

Ixodes ricinus Linnaeus 1758 —In Europe and South Africa The filtrable virus of louping ill can multiply in this species being transmitted probably to man sheep etc Experimentally it has transmitted *Rickettsia rickettsi* the cause of Rocky Mountain spotted fever

Ixodes ricinus californicus Banks 1904 —The bite of this species is very painful and irritating At times the mouth parts remain in the skin when it bites man causing secondary infection and serious reactions In North America chiefly in southwestern Oregon it transmits to rodents and to sheep by proliferation and by heredity the bacteria of tularemia

Ixodes hexagonus Leach 1815 —In Europe This tick can retain *Pasteurella pestis* for many days within its tissues

Ixodes bicornis Neumann 1906 —In Mexico The bite may be fatal to children It provokes a high fever in man

Ixodes pilosus Koch 1884—In South Africa It causes paralysis This occurs while the female of the species is feeding

Ixodes holocyclus Neumann 1899—In Australia It originates a morbid state which resembles paralysis caused by ticks in the United States Cases of paralysis occur chiefly on the eastern coast of Australia It may affect man sheep cats puppies etc In Australia it transmits *Rickettsia burnetti* the cause of Australian Q fever

Ixodes persulcatus Schulze 1930—The bite causes an inflammatory reaction The homogeneous zone surrounding the buccal parts of the tick is composed of eosinophiles free of nuclei This tick causes paralysis while feeding In Russia it is the reservoir and the transmitting agent of the virus of spring and summer encephalomyelitis

Ixodes scapularis Say 1821—North and Central America It may attack man

Ixodes ozarcus Cooley 1944—This North American tick frequently attacks man causing intensely troublesome effects

Genus Haemaphysalis Koch 1844

Haemaphysalis cinnabarina Koch 1844—This species found in western Canada and in Crete is believed to produce paralysis which may prove fatal It can transmit tularemia to several species of birds *In Asia it has transmitted* the organism of tularemia to rodents

Haemaphysalis leporis palustris Packard 1869—It transmits rickettsiae of Rocky Mountain spotted fever to different species of rabbits and to some birds principally game birds In the tick the microorganism is carried from stage to stage and it may also be hereditarily transmitted It is a potential transmitter to man Infected forms have been found in northeastern United States It has been demonstrated that it transmits *Pasteurella tularensis* to rabbits

Haemaphysalis bispinosum Neumann 1897—In New Zealand This species is considered as a potential vector in the cycle of Q fever

Haemaphysalis concinna Koch 1844—This is an American species which experimentally transmits rickettsiae of spotted fever

Haemaphysalis leachi Audouin 1827—The bite has a very troublesome effect upon man In Africa it transmits probably by development and heredity rickettsiae which cause a type of fever that is not relapsing In Africa it transmits biliary fever to dogs not only in the adult stage but by development and heredity In South Africa it transmits *Babesia canis* the cause of malignant icterus in dogs Transmission is effected by the larvae as well as by the nymphs and adults In Africa the species also transmits bovine piroplasmosis

Haemaphysalis humerosa Warburton and Nuttall 1909—In Australia It transmits Australian Q fever among the bandicoots

Genus Dermacentor Koch, 1844

Dermacentor reticulatus Fabricius, 1794.—Spotted fever may be transmitted experimentally by this species of tick.

Dermacentor variabilis Say, 1821.—It is found in the eastern United States and the Pacific coast. It produces paralysis. In these districts the nymphs and adults transmit to man by development and by heredity the rickettsiae of Rocky Mountain fever. In rural areas along the Atlantic Coast of the United States, as for example Connecticut and North Carolina, the species transmits a special type of spotted fever. It transmits *Pasteurella tularensis* to man *from the Rocky Mountains eastward in the United States*.

Dermacentor andersoni Stiles, 1908.—It causes progressive paralysis in children, sheep, dogs, rabbits, cattle, deer, etc., in North America, principally in western United States and Canada. Paralysis occurs while the female tick is feeding. In Australia there occurs a similar illness. Quite serious local lesions result in man due to the bite, but they are more frequently seen in cattle. Anemia is produced in cattle, sheep, rabbits, deer, and in general in those animals upon which great numbers of the tick feed. Several types of filtrable virus have been isolated from this species. In 1926 Noguchi reported a filtrable virus isolated from *Dermacentor andersoni* collected west of the Bitter Root Valley in the United States. In 1938 Davis and Cox isolated a virus which, according to their report, was probably the same as that of Noguchi. These viruses are transmitted from the adult to the egg and pass unaffected through the larval, nymph, and adult stages. They may cause infection in man. There is probably some relation between this infection and Australian Q fever. In North America several filtrable viruses have been experimentally transmitted to horses, causing encephalomyelitis. Transmission in ticks may be hereditary and is passed from stage to stage in the life cycle of the tick. The principal illness transmitted by this species of Dermacentor in the United States is Rocky Mountain fever. The rickettsiae of this fever are transmitted to man, horses, cattle, and sheep in such Rocky Mountain states as Montana and Wyoming, extending toward the Pacific. In ticks the transmission takes place by development and by heredity. The pathogenic agent is *Rickettsia rickettsi*. It is said that this species of tick also transmits endemic (murine) typhus. By intrarectal inoculation it keeps active for at least 14 days rickettsiae of endemic Mexican typhus. The tick also transmits *Rickettsia diaporica* of American Q fever to man and to some animals, and probably also the rickettsiae of Colorado tick fever. Experimentally it has transmitted *Salmonella enteritidis* as well as *Bartonella bacilliformis*, the cause of Oroya fever. In the United States it transmits *Pasteurella tularensis*.

Dermacentor occidentalis Marx, 1892.—This species is a potential transmitter to man of Rocky Mountain fever. In the United States, principally in California and Oregon, it transmits the bacteria of tularemia to man and to cattle.

Dermacentor parumapertus Neumann, 1901.—In the United States this species is the potential transmitter to man of Rocky Mountain spotted fever

t also transmits to rabbits the so called rabbit spotted fever In the United States it has transmitted experimentally the bacteria of tularemia

Dermacentor silvarum Olenev 1931—In Asia this species has transmitted the organism of tularemia to rodents experimentally and only from stage to stage

Genus **Otocentor** Cooley 1938

Otocentor nitens Neumann 1897—American species It transmits rickettsiae of endemic typhus

Genus **Rhipicephalus** Koch 1844

Rhipicephalus sanguineus Latreille 1804—This cosmopolitan species of tick produces serious local lesions in its host which is principally the dog The bite produces a pruriginous lesion which quickly disappears In India it causes intensive anemia in dogs Experimentally in Yugoslavia it has produced paralysis In Europe it has caused toxic icterus in dogs but the mechanism of this disease is not known Experimentally it has been proved capable of maintaining the virus of yellow fever in its tissues for several weeks It is a potential transmitter of United States Rocky Mountain fever In Mexico in the State of Sonora it has been found naturally infected with rickettsiae of Rocky Mountain fever It also transmits S o Paulo typhus in Brazil In Europe and in the Mediterranean regions it transmits by development and heredity *Rickettsia rickettsi conori* the cause of fièvre exanthematique fievre boutonneuse or Kumaon fever in these regions In Africa it also transmits the *Rickettsia rickettsi conori* the cause of the so called tropical typhus of Kenya or pseudotyphus of Kenya In Asia it transmits rickettsiae which cause tick typhus of India It is also considered as a potential vector of Australian Q fever Tick fever of South Africa is also attributed to its bite In Algeria and in the Mediterranean zone generally it transmits *Borrelia hispanica* the cause of Spanish relapsing fever In Iran it transmits *Borrelia theileri* to cattle and to sheep Experimentally it has successfully transmitted *Pasteurella tularensis* In South America it transmits *Trypanosoma cruzi* mechanically to armadillos *zarigueyas** and probably to domestic animals Neiva demonstrated that it transmits this microorganism indirectly When experimentally infected with *Leishmania infantum* the species maintains its virulence in the tissues for several weeks

Rhipicephalus simus Koch 1844—In East Africa it causes a febrile illness by its bite

Rhipicephalus evertsi Neumann 1897—From Australia and Africa In Africa it transmits spirochetes of relapsing fever both by development and by heredity

Rhipicephalus haemaphysaloides Supino 1897—It transmits rickettsiae of pseudotyphus in India

Rhipicephalus schulzei Olenev 19?0—A Russian species It is capable of retaining the bacillus of plague in its digestive tube for several days

* A small marsupial about the size of a cat

Genus Boophilus Curtice 1891

Boophilus annulatus Say 1821 —American species It may parasitize man causing very troublesome local lesions

Boophilus microplus Canestrini 1887 —In South America it is probably the transmitting agent of spirochetes of relapsing fever

Genus Hyalomma Koch 1844

Hyalomma dromedarii Koch 1844 —In Yugoslavia it has experimentally produced paralysis In Sicily the bite causes local inflammation of an erysipelatous aspect with suppuration lymphangitis and high temperature accompanied by delirium It can transmit the bacillus of plague

Hyalomma volgense Schulze and Schlottke 1929 —This species is capable of transmitting plague by its bite and infective excretions

Genus Amblyomma Koch 1844

Amblyomma ovale Koch 1844 —In Paraguay it is assumed that this tick is capable of transmitting American cutaneous leishmaniasis

Amblyomma maculatum Koch 1844 —Parker Kohls Cox and Davis (1939) isolated a rickettsiform organism from this tick removed from cows in Cleveland Texas Cox (1941) cultivated in the ticks collected in Texas and Georgia the rickettsiae of petechial fever of Tobia in Colombia It also transmits a rickettsia which is very similar to that of fièvre boutonneuse

Amblyomma americanum Linnaeus 1758 —Its bite causes suppurations which leave an inflamed itching zone that may persist for several weeks In the United States this species is the potential transmitter of Rocky Mountain fever By means of this tick American Q fever has been transmitted experimentally to guinea pigs In Texas it is believed capable of transmitting a new disease known as Bullis fever the pathogenic agent of which is a rickettsia In North America it transmits bacteria of tularemia to rodents and sheep by proliferation and by heredity Experimental transmission has also been effected

Amblyomma cajennense Fabricius 1787 —The bite of this species is very irritating and painful It frequently causes an ulcer which cicatrizes only with difficulty The pruritus lingers for weeks In South America experimental transmission by means of the bite has been successful in transferring the filtrable virus of yellow fever although this work has not been fully confirmed Transmission to primates has been effected In the United States it is a potential transmitter to man of Rocky Mountain fever In South America it transmits by development and heredity *Rickettsia brasiliensis* the causative agent of São Paulo typhus In the State of Minas Geraes, Brazil Moreira and Magalhaes have transmitted a disease which is analogous to this fever and which is transmitted by this species of tick It is also the transmitter of Colombian spotted fever The species is capable of retaining for some time the bacilli of tuberculous leprosy In South America the species mechanically transmits *Trypanosoma cruzi* the causative agent of Chagas

disease to armadillos *zarigueyas*, and possibly also to some domestic animals It may also transmit *Leishmania braziliensis* Moreover, it serves as the vehicle for eggs of *Dermatobia cyaniventris*, the larvae of which produce cutaneous myiasis in man and animals

Amblyomma striatum Koch 1844—It transmits, by development and heredity rickettsiae of Sao Paulo fever in South America

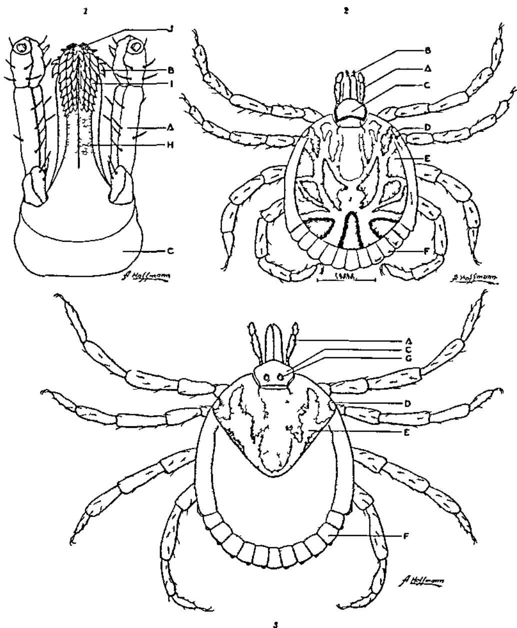


Fig 427—*1* Mouth parts *2* dorsal view of male and *3* ventral view of female of *Amblyomma cajennense* (Fabricius) *A* Palpus *B* chelicerae *C* base of capitulum *D* eyes *E* shield *F* festoons *G* porous area *H* hypostoma *I* teeth of hypostoma *J* corona of hypostoma.

PROPHYLAXIS

The best way to prevent disease and all lesions caused by ticks is to take measures to avoid being bitten by them. When the bite has already occurred, it is important to detach the tick from the skin as quickly as possible, since each moment increases the danger of transmission of some disease organism, whether it be Rocky Mountain fever or others. Several means for withdrawing the tick from the skin are employed. Heat, phenolized petroleum jelly, etc., may be used, although they are not always effective.

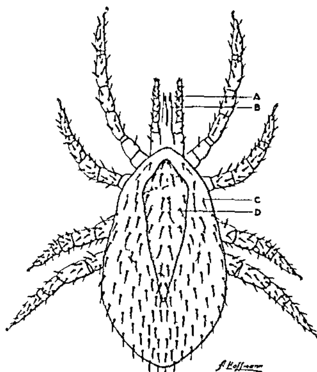


Fig. 4-5.—Dorsal view of *Liponyssus bacoti* (Hirst). *A*, Palpi. *B*, chelicerae. *C*, peritrema. *D*, shield.

Contact with ticks may be avoided by keeping away from infested places, which are, for the most part, areas covered with vegetation and frequented by hosts of the acarids. High boots, long stockings, gloves, etc., should be worn. When camping out, places which are not covered with vegetation, especially of the herbaceous type, should be chosen. In camping out, one should sleep in a hammock to avoid direct contact with the ground. A minute examination of the clothing should be made several times a day.

Small areas can be cleared of ticks by depriving them of their hosts for 1 or 2 years. If possible, rodents in these areas should be destroyed by poison and by trapping. Grass and herbaceous vegetation around dwellings, schools,

parks and other places frequented by the public should be kept cut short Dogs and other domestic animals that serve as hosts for this acarid should be kept out of infested areas and repellents and insecticides should be used regularly

Superfamily PARASITOIDEA

Family **LIPONYSSIDAE**

Representatives of this family are distributed widely throughout the world but are localized principally in hot climates The best known species is *Liponyssus bacoti* (Hirst) 1913 a common mite of the rat Other species of the genus also attack man causing intense dermatitis Examples of these include *L bursa* (Berlese) 1888 *L nagayoi* Yamada 1931 and *L sylviarum* (Canestrini and Fanzago) 1877

L bacoti feeds entirely on blood dropping from the host after feeding

These mites are very active Their distribution is closely linked with that of rats They attack man when he frequents sites where the rodents are found

The bite is painful usually urticaria papules and vesicles appear at the site Intense pruritus is present with small hemorrhagic areas Secondary infection due to scratching readily occurs especially in children It has been demonstrated that this species of mite is capable of transmitting murine typhus *L nagayoi* is considered potentially dangerous as the vector of bubonic plague

Dermatitis may be caused by ***Dermanyssus gallinae*** (Linnaeus) a parasite of birds From it has also been isolated the virus of equine encephalomyelitis Several species of Laelaps such as *L stabularis* Koch and *L echidninus* Berlese of the family Laelaptidae are important medically

Superfamily TROMBIDOIDEA

Family **TROMBIDIIDAE**

Adult mites belonging to this family are brilliantly colored They are easily identified by the slight separation between the cephalothorax and the abdomen

They are widely distributed in tropical and subtropical regions They are parasitic only in the larval stage the nymphs and adults being predatory and free living Larvae parasitic for man and vertebrates have been grouped within the subfamily Trombiculinae

Trombidids deposit eggs on the ground From these emerge tiny hexapod larvae of a bright red color They can immediately set about to parasitize their hosts including man Because of their small size they are readily introduced under clothing and attack the skin of the host They introduce only the mouth parts attaching themselves to the host usually at the base of a hair

After alimentation the larva drops from the host and falls to the ground where it molts and is transformed into a nymph and later into an adult. Only one generation develops in a year.

Larvae feed principally upon lymph found near the epidermis and, occasionally, upon blood. The presence of these animals is scarcely noted at first. The bite produces a small red area with intense pruritus, very annoying, which may last for several days. The smarting sensation is probably due to injection of a hemolytic fluid which is secreted by the salivary glands. Sometimes the blood from the subcuticular capillaries is extravasated, producing a purplish or bluish ecchymosis which may persist for several months. Secondary infection frequently develops from scratching the bite. There is in Mexico a well known parasitic affection, "tlalsahuatosis," characterized by wheals and papules and accompanied by intense pruritus. This affection is produced by the larvae of trombidids commonly called "tlalsahuates."

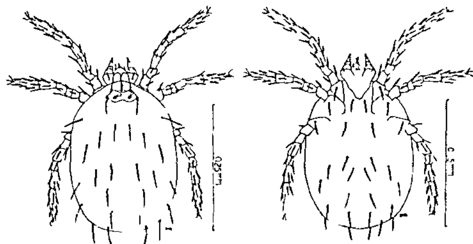


Fig. 4 9.—Dorsal (left) and ventral (right) views of *Neoschoengastia nunezi* Hoffmann. (From Rev. Inst. Salub. y Enferm. Trop. 5: 2?1, 2 ... 4.)

This name includes several species, among which are found *Eutrombicula alfreddugesi* Oudemans 1910 and *Acariscus flui* van Thiel 1930. The first species is the most common in Mexico and in North America and appears during rainy periods. The mite prefers domestic animals such as rabbits, mice, rats, fowl, etc. Fowl frequently die due to the bite of this mite. Accidentally the species may also attack man. In Mexico another species has been found, the *Neoschorngastia nunezi* Hoffman 1944, which causes dermatosis in man.

In other parts of the world there are trombidids which are even more harmful. In Japan, Formosa, Sumatra, Malaya, Australia, India, New Guinea, Burma, and adjacent regions, the larvae of these mites transmit tsutsugamushi (scrub typhus). The Rickettsiae are harbored by small rodents, especially field mice, which are their natural reservoirs. In Japan and the neighboring regions *Trombicula akamushi* transmits *Rickettsia orientalis*. In Sumatra

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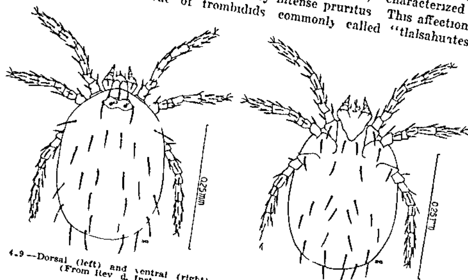


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T deliensis a mite very much like *T akamushi* is known also *T hirsti* *T scutellaris* and *T schuffneri* The infectious agent is transmitted only by larvae but the infectious agent survives in the body of the trombidiid through the nymph and adult stages passing into the eggs of the next generation

Other trombidids which have been reported as harmful to man are *T hirsti* in Australia *T wichmanni* in the Celebes and in New Guinea and *Leeuwenhoekia australiensis* in New South Wales In Europe *Trombicula autumnalis* has been cited This species in addition to attacking man has also been taken from horses cattle dogs cats rabbits etc

PROPHYLAXIS

Destruction of vegetation in the infested area seems to be the most practical means of control of rural typhus When the surface of the ground has had time to dry out the area may be considered safe

The most effective means of protection against mites consists of application of repellent fluids (dimethyl phthalate benzyl benzoate etc) to clothing sprinkling or submerging the clothing in the solution A method which gives apparently satisfactory results is the immersion of clothing in an emulsion of 5 per cent dimethyl phthalate and 2 per cent soapsuds Griffitts (1943) indicated that this measure is not 100 per cent effective when it is necessary to sleep on the ground or in trenches or when wearing socks not treated with the solution

The value of sulfur and sulfur ointment applied to the skin to kill larvae of trombidids has been known for a long time Since itch has at times been confused with dermatosis produced by the larvae the sulfur treatment used for itch must have killed many trombidiid larvae Dusting with 2 per cent DDT is also very effective Ewing (1944) reported that DDT seems to be the best acaricide when it is used on the first day that sulfur is best when it is applied on the seventh day and that on the third day both substances are of about the same value Yeager and Wilson (1944) spoke of a new remedy for pruritus which results from the bite of so many of these pests It is called Circa 42 and is composed of the following ingredients

n butyl p aminobenzoate	100 Gm
benzyl c alcohol	170 c c
anhydrous lanolin	90 c c
corn meal	640 Gm
sodium lauryl sulfate	64 Gm

Superfamily TARSONEMOIDEA

Family **PEDICULOIDIDAE**

This family is of interest from a medical standpoint because of the species *Pediculoides ventricosus* (Newport) This predaceous acarid which attacks the larvae of numerous insects can also attack man causing a dermatitis

Pediculoides ventricosus penetrates within the epidermis of man often producing petechial hemorrhage and erythema Vesicles and pustules occur around

the affected site The area shows a violet tinted discoloration Sometim these lesions cover the greater part of the body producing a very vexaciou pruritus There may be a rise in body temperature and a great deal of per spiration Applications of hot water and mild antiseptics may partially allay the burning sensation

As a measure of control of these mites it is best to burn infested seed grain etc and if possible the places where these have been stored

Superfamily TYROGLYPHOIDEA

Family **TYROGLYPHIDAE**

The representatives of this family are some few acarids which infest foodstuffs such as cereals grains and especially cheese Many of them feed upon decomposed organic substances and a few are parasitic

They are very small The chelicerae are in most cases provided with chelae the legs terminate in claws and small caruncles

The dermatitis caused by these mites in man is similar to that caused by *P ventricosus* Some species as *Tyroglyphus longior* have been found in the intestinal and urinary tracts

When the mite is ingested with the infected food especially cheese it may later be found in fecal matter it is not known however that the mite causes a true intestinal infestation

Superfamily SARCOPTOIDEA

Family **SARCOPTIDAE**

Within this family are included those mites responsible for itch in many species of mammals and birds Twelve genera are known Of these only the genus Sarcoptes has been found to infest man The best known species is *S scabiei* (Linnaeus) 1758 which localizes in or on the skin of its host

Organisms of this genus are usually semicircular The body smooth for the most part has bristles that are remarkably long in relation to the size of the animals and has short pointed spines In the female the tarsi of the first and second pairs of legs provided with suckers are continued into long lender unsegmented pedicels In the male these tarsal suckers are present n the first second and fourth pairs of legs In the male the anus is terminal nd lacks anal suckers The species lacks eyes and tracheae

Sarcoptes Scabiei

Sarcoptes scabiei is a very small mite The female measures approximately) microns in length by 275 microns in width while the male is about by 165 microns The mite is of a whitish color the cuticle having y fine transverse striations interrupted here and there by a few bristles spines The legs are very short the third and fourth pairs in the female long bristles The 2 anterior pairs are quite apart from the 2 posterior

pairs Buccal parts consist principally of a pair of very small chelicerae and a pair of short trisegmented palpi

Life Cycle—The gravid female infests the skin through intraepidermal channeling depositing her eggs in small groups 15 or 20 at a time The eggs measure about 160 microns in length After oviposition the female dies at the end of the tortuous channel After a period of 3 to 6 days small hexapod larvae emerge from the eggs They leave the maternal channel and proceed

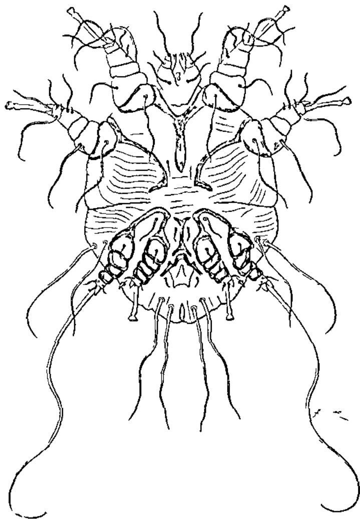


Fig 430—Ventral view of *Sarcoptes scabiei* (Linnaeus)

to form new superficial papules in the skin originating a new channel and burrowing generally among the hairs without however penetrating the hair follicles After 2 or 3 days the larvae are transformed into the first nymph stage characterized by 4 pairs of legs In this stage they may remain in the same site or they may move to another location to form a new epidermic papule They molt again emerging as male and female forms Mating is

effected on the surface of the skin, after which the female penetrates the skin and the cycle is renewed The female lives for 3 to 4 weeks, which is about the length of time it takes to complete the life cycle from adult to adult The male exists for a shorter period, and it is thought that he remains for the most part upon the surface of the skin

Infection is disseminated when the mites, after any of the molts, are at the surface of the skin It is spread by direct contact or by clothing Some authors believe that the most important stage in dissemination is the fertile female It is easy for the female to localize on the surface of the skin, especially when the skin is warm—for example, when the host is sleeping

The mite may penetrate through the skin in almost any region of the body It localizes, principally, in such areas as the interdigital spaces, on the back of the hand on the wrists in the groin in the external genital organs, in the elbows the axillae breasts, shoulders, and parts of the neck

Intense pruritus, which is the principal characteristic of the disease, begins approximately 10 days after infection It is believed that the pruritus is due more to mechanical irritation than to an irritant secretion of the mite Lesions in the skin develop rapidly due to the short life cycle of the Sarcoptes and the rapid succession of generations

The first observable sign on the skin is a reddish line slightly elevated along the surface of the skin With the aid of a hand lens a tiny orifice can be distinguished, and the presence of a vesicle very small, at the end of the tract near which the female is found Scratching readily produces complications such as secondary infection pustules excoriation sometimes eczema, etc

TREATMENT

Thirty per cent benzyl benzoate is very effective, usually one application is sufficient after a hot soap and water bath Tetraethylthiuranum monosulfide in the form of a solution of Tetmosol, in a dilution of 1 plus 3, is one of the present day treatments used for "itch" in children Bradshaw (1944) reported rapid cure in 97 per cent of his cases after only 3 days of treatment Treatment is painless with only slight risk of dermatitis

Mellanby, Johnson and Bartley (1942) in their summary of treatment of "itch" indicated that a single thorough application of Marcussen's ointment, a 10 per cent sulfur ointment a 10 per cent solution or stronger of benzyl benzoate in alcohol or water, or even better, a solution of dimethyl diphenylene bisulfide, killed more than 98 per cent of the parasites Also efficacious although to a lesser degree, are substances like pyrethrum, emulsion of Rotenone solution of derris root, beta naphthol, or lethane

Regardless of the preparations used care should be taken to disinfect the clothing and the bedding of the patient All members of the family should receive treatment as soon as possible The best prophylaxis against the "itch" is avoidance of contact with infected individuals, with public towels, or unclean sheets

Superfamily DEMODICOIDEA

Family **DEMODICIDAE**

In this family are grouped all those mites which parasitize the hair follicles or sebaceous glands of mammals The family comprises only one genus Demodex which includes a few species One of the best known and most studied species since it affects man is *Demodex folliculorum* (Simon)

Demodex Folliculorum (Simon)

This is a very small mite worm like in appearance due to its elongated abdomen The abdomen is marked with numerous very fine transverse lines The head is short and broad and the 4 pairs of legs are greatly reduced The mouth parts are degenerated and grown together Palpi are trisegmented with very small curved chelicerae adapted for biting Anus is lacking The female measures approximately 0 35 to 0 40 mm and the male is smaller

Reproduction is very slow The larvae alone are provided with 3 pairs of tubercle like legs Four molts are necessary for the mite to pass from the larval to the adult stage

The presence of this acarid in the skin of man is a frequent occurrence but it is of no great significance At times it produces chronic erythema with drying of the skin and follicular desquamation accompanied by a burning sensation Women are more frequently affected since they often use facial cleansing creams instead of soap on their skin

TREATMENT

Scrupulous cleanliness should be practiced Various ointments such as balsam of Peru etc may be applied locally Ultraviolet ray treatments and antistaphylococcus vaccines are sometimes used with uncertain results

Order **Pedipalpida**

These arachnids are recognized by the fluid which they secrete in defense and as a repellent The fluid has a characteristic vinegar like odor for which reason they have been given the name of vinegerone or vinagrillos in Latin America They are called whip scorpions in English

They differ from other arachnids principally in the flagelliform aspect of the first pair of legs and also in some species by a whip like appendage found in the last abdominal segment The abdominal segments are wide These arachnids are found in dark hiding places and inhabit exclusively the tropical and semitropical regions of the Old and New Worlds

Pedipalpids do not bite The liquid which they secrete may cause a *troublesome irritation to individuals with sensitive skin Otherwise the animals are inoffensive*

Order **Solpugida**

Representatives of this order differ from true spiders in having a segmented abdomen in addition the union of the cephalothorax and abdomen is wider Chelicerae are provided with 2 large sturdy segments Their bite

though painful, is not harmful, since they possess no poison glands Occasionally, the wound may be deep enough to admit bacteria, resulting in a secondary infection

These solifuges live, principally, in tropical and subtropical regions Most of them have nocturnal habits, there are some which prefer sunlight, but they are so swift in their movements that it is very difficult to trap them They feed principally on insects

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CHAPTER 56

POISONING BY SCORPIONS AND SPIDERS (SCORPIONISM AND ARANEISM)

AFRANIO DO AMARAL

SCORPIONISM

INTRODUCTION

Scorpions are veneniferous animals belonging to the phylum Arthropoda, class Arachnida, and order Scorpionida Like all Arthropoda, they are articulated the body being provided with metameric segments and bearing jointed limbs They have a cephalothorax resulting from the coalescence of the head with the thorax, and in this they differ from the insects, they have 4 pairs of legs in this differing from both the insects and the myriapods, and sessile eyes in this differing from the crustaceans They have a long and segmented abdomen *differing from the spiders, the abdomen of which is short and unsegmented*

With the cephalothorax of scorpions are connected both the locomotive and the prehensile appendages The former consist of 4 pairs of legs, each leg divided into 7 segments coxa, trochanter, femur, tibia, and 3 tarsal sections The latter consist of 1 pair of chelicerae and 1 pair of pedipalpi The chelicerae or jaws are rather minute and are covered by, or hidden under, the anterior border of the cephalothorax or prosoma, each chelicera ends in a small chela or nippers with no venom gland The pedipalpi or maxillary palpi are quite long and strong and are divided into 5 segments, of which the terminal segment corresponds to a pair of larger pincers or claws

The abdomen is divided into 2 portions anterior or mesosoma with 7 joints, and posterior or tail with 6 segments, of which the terminal segment bears the vesicle with 2 venom glands and tapers gradually to a sting

Scorpions usually carry the tail bent back up over the body At the moment they try to catch a prey or reach an enemy, they bend the tail forward, so as to bring the tip or sting to the level of the pincers of the pedipalpi, the function of which is to hold the prey at that moment Except for the sting and the venom, scorpions would be entirely defenseless

The body is covered with a hard chitinous shell The brain is connected with a chain of ganglia ventrally situated The heart is elongated and extended into an artery both proximally and distally

CAUSAL AGENTS SCORPIONS

Scorpions are rather unsociable animals, usually to be found under stones, in the crevices of rocks and walls, among pieces of wood and shingles, brick piles, or in closets where they seek to hide inside of shoes and dresses They

are extremely secretive, leaving their haunts only at night They live mostly in tropical and subtropical countries, where they seem to prefer warm and dry climates but cannot withstand exposure to the hot sun

They are represented in tropical and subtropical sections throughout the world and in some temperate districts by numerous species the lengths of which vary quite widely being from 2 to 20 cm or more

Among the hundreds of species of scorpions the following deserve special mention, either because of the size they may attain and the amount of venom they can secrete, or the high density of their respective populations in various tropical districts

Scorpio imperator or "Escorpião do Gabão" (gabon scorpion), found in west central Africa, it is the largest form thus far recognized, as it reaches a length of more than 20 cm

Buthus quinquestriatus, prevalent particularly in northern and eastern Africa it is also very large and causes many accidents in the Nile valley



Fig 431 —A common scorpion with the abdomen (tail) raised so as to bring the sting (terminal segment) forward

Rhopalurus baiuthenar, a large form the range of which covers the central section of South America Colombia, and Central America

Tityus bahiensis, a medium sized form spread throughout Brazil and the southernmost republics, where it is responsible for the majority of cases of scorpionism *T serrulatus,* a common form, found in the central plateau of Brazil

Bothriurus bonariensis, a rather small form, although quite common throughout the subtropical and temperate districts of eastern South America

In the Western World, from Panama northward, there also occur a few more species of Tityus and some 12 or more species of Centruraides, or Rhopalurus, among the Buthidae and from Colombia southward, are found over twenty species of Tityus and nearly as many of Rhopalurus, among the Buthidae, besides *Thestylus glasioui* and other species of Bothriuridae and *Diplocentrus gundlachi* among the Scorpionidae

Isometrus maculatus like other congeneric species is native to India whence it has spread apparently through transoceanic traffic and in recent times to south Europe Africa and the Americas

The common name for scorpions is alacran throughout the Spanish American countries and lacrau in Brazil

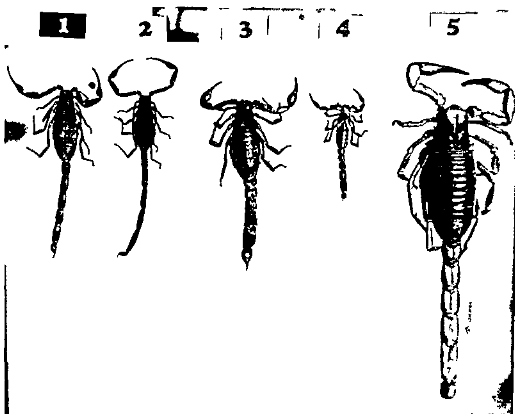


Fig 432—Various species of scorpions *1* and *2* *Centruroides sculpturatus* male and female *3* and *4* *Vejovis spinigerus* adult and young *5* *Hadrurus arizonensis* (From Merck Report July 1946 from article by Stahnke Herbert L Some Poisonous Animals of the United States by permission of the author and publisher) (Photograph by Stahnke)

POISON APPARATUS AND VENOM

The sixth or terminal segment of the tail or metasoma of scorpions is represented by a globose vesicle extending posteriorly along the body axis gradually becoming thinner and thinner until it ends in a sharp spine curved toward the ventral side This vesicle holds a pair of venom glands the ducts of which open on each side of the spine close to the tip

The poison is clear and watery at first becoming rather milky and sticky as soon as the drops from the lumen of the gland have been ejected It has a slightly acid reaction is insoluble in ether and absolute ethyl alcohol and resists neutral glycerin and chloroform It is destroyed in vitro however by gold chloride calcium chloride ammonia potassium permanganate and

Lugol s solution It is thermostable up to 70° C for 1 hour In solution it is precipitated by sodium magnesium and ammonium sulfates this reaction indicating its proteinaceous character It has no action when given per os it is destroyed by the digestive secretions

Although very little has been done regarding the real nature of the chemical constituents of scorpion venoms it is known that they vary from species to species and that they represent a mixture of several toxic and antigenic principles the specificity of which is also very marked

The amount of venom a scorpion is able to eject varies quite widely according to the species the age and size of the specimen etc Usually, when it stings naturally and spontaneously the scorpion expels but 1 or 2 small drops of venom never emptying its glands but keeping some of the venom for emergencies If hard pressed or squeezed by forceps for instance it will let 1 or more drops exude and then give up the fight The first drops however are always more toxic than the last ones

A common trait of all scorpion venoms is the presence of neurocytolysins or neurolysins both for the central nervous system and for the autonomic system It is the ratio of the different principles of this group that gives the venom of every form a certain degree of specificity towards the animal tissues

Moreover in some species such as the African *Buthus australis* and *B occitanus* and the Brazilian *Tityus serrulatus* the venom appears to contain a certain proportion of proteolysin and hemolysin as revealed by some swelling at the site of the sting followed at late stages of venenation by blood extravasation into the stomach and intestines (hematemesis and melena) and the kidneys (hematuria) Destruction of the corresponding epithelium is present in patches in every case of this type of poisoning None of these symptoms however is ever so accentuated as to overshadow the general picture of neurotoxicosis always present in scorpionism

CLINICAL SYMPTOMS

In most cases of scorpionism the principal symptoms may be divided into local and systemic

Local Symptoms

Pain sometimes unbearable and usually extending along the affected limb to the chest is the first sign following contact of the sting with the human skin A reddish white-centered wheal surrounding the single puncture may eventually be noticed later spreading into an edematous area either serous or bloody in character Finally lymphangitis is not a rare occurrence These symptoms constitute the invasion period of the poisoning

Systemic Symptoms

Bradycardia as a central nervous reflex to the pain constant sneezing watery nasal discharge and bronchorrhea profuse lacrimation mydriasis nausea vomiting and diarrhea abundant perspiration and cold sensation dizziness and trembling are the symptoms in the excitation period of the poison

ing in which the neurolysin of the venin apparently acts upon the sympathetic nervous system This neurotropic peculiarity warrants classification of the principal neurotoxin of the scorpion among the sympathomimetic or adrenergic substances It really seems to cause an initial discharge of epinephrine into the blood stream soon to be followed by marked peripheral vasoconstriction and increased blood pressure Stimulation of the cervical sympathetic nerve can explain such signs as mydriasis hypothermia of the skin and vasoconstriction particularly accented over the entire head hypersecretion of the nasal mucosa and the lacrimal salivary and sweat glands Dilatation of the bronchi with mucus discharge gastrointestinal hypersecretion and contractions (increased peristalsis) dizziness and trembling may show how deeply the autonomic system is affected at this stage

In susceptible patients particularly nervous children and whenever the volume of venom injected is large enough there is a final period of depression consisting of symptoms which show the direct effect of the neurolysin upon the central nervous system exaggeration of the reflexes (patellar especially) clonic contractions convulsions hiccup sensation of throat constriction headache delirium tachycardia (up to 180 pulsations per minute) and low blood pressure dyspnea (usually of the Cheyne Stokes type) loss of equilibrium purplish lips increasing hypothermia coma and sometimes death

As sequelae of the venenation when the patient recovers naturally there may appear numbness of the limb where the sting was inflicted hyperesthesia and eventually hemiplegia or paraplegia

Finally in poisoning caused by the sting of certain species (*Buthus occitanus B australis* and *Tityus serrulatus*) the clinical picture may be aggravated by such symptoms as hematemesis melena and hematuria which prove the destructive effect of proteolysin and hemolysin on the epithelial covering of the gastrointestinal tract and the kidneys and on the endothelial layers of the capillaries as well

DEATH RATE

Although the incidence of scorpionism is fairly high in certain districts of central Brazil Central America Egypt and Korea the death rate is relatively low It must be borne in mind however that scorpion venoms like all toxic substances act on the body in a manner inversely proportional to the weight that is the smaller the patient the greater the concentration of the same dose of venom No wonder therefore that scorpions take a higher toll of lives among children than among adults

PREVENTION OF SCORPIONISM

The various means devised to prevent scorpion stings are of 2 groups (1) individual protection and (2) collective protection

Protection of the Individual

In any scorpion infested district children should be induced not to play or stay around sites where these Arachnida are known to seek shelter Care must be taken to prevent being stung while putting on shoes or boots coats or other pieces of clothing left in dark closets Finally one must be particularly cautious in handling shingles pieces of wood and other objects taken during the day off piles where scorpions may be hiding

Individual protection can also be secured by preventive immunization with antivenins specific for the species prevalent in certain sections

Collective Protection

Collective protection may be achieved to a certain degree by use of chickens which are left to range freely over any place where scorpions are abundant Chickens not only have a little natural immunity against some scorpion venoms but they seem to like to attack scorpions which they kill with extreme readiness without being stung

TREATMENT OF SCORPIONISM

Therapeutic means directed at counteracting the effects of scorpion venoms on human tissues are divided into 2 categories (1) nonspecific measures and (2) specific procedure

Nonspecific Measures

In view of the sympathotropic effect of the venoms administration of any strong heart stimulant must be avoided at least during the excitation period of the poisoning Application of a ligature above the site of the sting is of no avail since the venin is largely absorbed by the nerves Free bleeding and suction of the region where the sting was inflicted give the patient no relief because the venin is absorbed too rapidly to warrant such measures Potassium permanganate has no effect in vivo and causes local necrosis which should be avoided by all means

Whenever a specific antivenin is not available the treatment should follow quite closely the physiopathologic evolution of the venenation At the invasion stage the reasonable thing to do is to inject about the sting mark 1 or 2 cc (1 ampule) of magnesium sulfate solution with novocain (magnesium sulfate 25 per cent distilled water 74 5 per cent novocain 0 5 per cent) preferably by the hypodermic route since the venom is inoculated rather superficially due to the shortness of the scorpion terminal spine In the excitation phase in order to counteract the adrenergic effects of the venin injections of acetylcholine usually bring the patient some relief by acting on the posterior ganglionic fibers of the parasympathetic nervous system In the final or depression period the administration of cardiotonics while the sedative effect of the magnesium sulfate on the central nervous system is still noticeable usually brings some relief particularly when supplemented by liberal doses of salt

solution (physiologic saline) given WARM and SLOWLY by the venous route, and glucose solution or Ringer sodium acetate solution also injected WARM and SLOWLY into a vein In mild cases it is sufficient to give the patient an intravenous injection (10 c c) of a 10 per cent calcium gluconate solution to relieve pain In rare cases, when there is reason to believe that an acute pancreatitis complicates the clinical picture completing the treatment with 5 to 10 units of insulin is indicated

By enhancing the elimination of the venom while the resistance of the patient is sustained by rational measures, we can save many cases, even those of the greatest severity

Specific Procedure

When specific antivenin is available, it must be given at once, either hypodermically or intravenously, depending naturally on the severity of the case, the dosage always being greater for children than for adults

Since Todd (1909) proved that passive immunity can be conferred by application of serum of horses actively immunized against the venom of the Egyptian scorpion *Buthus quinquestriatus*, a few laboratories have been engaged in preparing antivenins specific against local forms In this connection, C Phisalix had shown in 1896, in the course of experiments with the venom of 2 types of African scorpions, that specificity is very close and Maurano (1915) confirmed Phisalix' observations and also proved the possibility of immunizing horses against the venin of the Brazilian *Tityus bahiensis* Brazil (1918) began the routine preparation of antiscorpionic serum, the potency of which he succeeded in increasing through concentration and globulin fractionating by taking advantage of the fact that the antitoxic fraction is bound to pseudoglobulin in the immune plasma The usual doses are 10 to 30 c c children requiring a larger amount of antivenin than adults, because of their lower weight, to neutralize the relatively greater concentration of the venom in their systems

Successful results have recently been reported by Sinson (1931) with the use of Crotalidic Antivenin (anti "snake bite" serum as prepared by the Antivenin Institute of America against rattlesnakes copperhead, and moccasin of the United States) in 2 cases of scorpion toxicosis Unfortunately, so far as the author knows his findings have not yet been confirmed

ARANEISM

Spiders, like scorpions are veneniferous animals belonging to the phylum Arthropoda and class Arachnida They are placed in the order Araneida, not *among the Scorpionida as scorpions are They differ from scorpions in having* a short unsegmented, usually globose abdomen the end of which presents a web spinning apparatus, consisting of 2 or more pairs of spinnerets rather short, leg like pedipalpi or maxillary palpi, and a pair of enlarged chelicerae or jaws each ending in a fang and containing a venom gland

CAUSAL AGENTS SPIDERS

Spiders are also secretive unsociable animals which live in and seek shelter under dead trees dry leaves and stems particularly during the summer months Sometimes they invade barns stables toilets and houses where they find insects on which they feed They also prey on mice small snakes lizards and birds In whatever site they choose to live they customarily spin threads of silk and make cocoons for their eggs nests for themselves or webs for entangling their prey

Although they are most active in hot weather they are found not only in tropical and subtropical regions but in temperate countries as well In some agricultural districts they represent a real scourge both to human beings and to animals especially during the crop season Their bites are most dangerous and sometimes deadly to children as well as to sheep goats and dogs

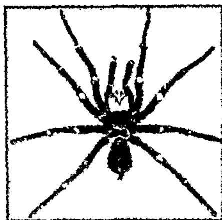


Fig 433 —Male tarantula spider Paper inserted to show position and size of fangs. Ventral view (From Merck Report July 1946 from article by Stahnke Herbert L Some poisonous animals of the United States by permission of the author and publisher) (Photograph by Bertram M. Freman and Herbert L Stahnke)

They are represented by numerous species of variable sizes but can be divided into 2 principal groups the Aranomorphae the true spiders sometimes called tarantulas and the Mygalomorphae or mygales the former possessing but one pair of pulmonary plates or lungs (Dipneumones) the latter bearing two pairs (Tetrapneumones)

Although popular names are usually meaningless the common mygale being very conspicuous because of its large size and hairy body and legs is called trap door spider in the United States aviculaire in Martinique caranguejeira in Brazil nhandu kabayu in Paraguay asipanea in Argentina arana pollito in Chile these names representing different species from a systematic standpoint A biologic characteristic of the mygales is that they do not spin true webs in which to live but use holes in the ground or among bamboo roots and there they make their silk tubes provided with a

trap door An anatomic characteristic of these spiders is that they bear short venom glands (each gland completely included in the corresponding fang) and fangs which move vertically The Mygalomorphae are divided into a few families of which the most representative are the Theraphosidae and the Ctenizidae, both with several genera and species of which the following deserve mention *Acanthoscuria sternalis,* found in south Brazil, Paraguay, Argentina, *Avicularia avicularia,* the bird spider, very common in South America, *Avicularia vestiaria,* from Martinique, *Cteniza sauvagei,* from southern Europe, *Eurypelma hentzii,* from southwestern United States and Mexico, *Grammostola acteon,* from the middle section of South America, *Lasiodora curtior,* from Brazil and tropical South America, and *Theraphosa blondii,* from Santo Domingo and Haiti

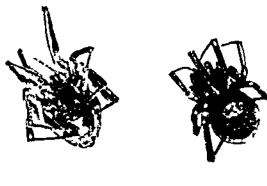


Fig 434—Black widow spiders (females) *Latrodectus mactans* From the collection of V Lewitus (From Merck Report July 1946 from article by Stahnke Herbert L. Some Poisonous Animals of the United States by permission of the author and publisher)

The Aranomorphae, or true spiders, which are known by many different names in different parts of the world, can be distinguished from the Mygalomorphae by the presence of elongated venom glands, each gland being longer than the corresponding fang in which it is included anteriorly, and by fangs which move horizontally They are divided into a few families of which the most representative are the Theridiidae, the Lycosidae, the Epeiridae, and the Pholcidae, of which the following genera and families deserve mention *Araneus audax,* from the middle section of South America, *Ctenus nigriventer,* from central South America, *Epeira diadema,* common in the Antilles, *Lycosa raptoria,* abundant in southern Brazil, Uruguay, and Argentina, and *Latrodectus mactans,* spread throughout the Americas (although rare in Brazil), where it has received the names of "araña de liño" in Argentina, "guina" in Chile, "lucacha" in Peru "casampulga" in Central America, black widow or hour glass spider in the United States The genus Latrodectus is also represented by several other species such as *L geometricus* in Brazil, *L hasselti* in Australia and New Zealand (common name "katipo"), *L lugubris* in southern Russia (common name, "karakurt"), *L tridecimguttatus* in southern Europe (common

name "malmignathe") *L. menavodi* in Madagascar (where under the name of "vancoho" it is considered sacred and so worshiped and protected by the natives) *Glyptocranium gasteracanthoides* is the technical name of "poda dora" a common form in the Peruvian vineyards and agricultural fields

INOCULATION OF POISON

Like scorpions spiders use their venom both to catch their prey quickly and to free themselves from attack by powerful enemies To seize an insect for instance spiders jump at it and try to inject the venom just behind the head so as to reach the cervical ganglia directly causing instant paralysis of the prey

Some species which live in agricultural fields or in habitations of human beings always represent a potential danger The female *Latrodectus mactans* particularly frequently spins her web across the seats of outdoor toilets in many sections of the Western World making it hazardous to use these installations

The female spider is responsible for the greater number of bites She is usually larger than the male which she kills as soon as she has been fertilized

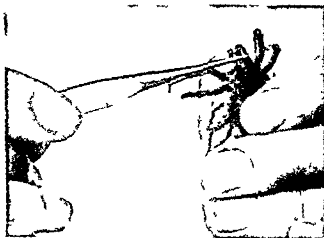


Fig 435—Pulling off the chelicerae (with venom glands and all) from a true spider (*Lycosa raptoria*)

POISON APPARATUS

The poison apparatus consists of a pair of glands and fangs Each gland is partly or wholly included in the chelicera or jaws of the corresponding side The poison is ejected through a slender duct which terminates in a hole or opening very close to the tip of the fang or claw Each gland is also composed of an internal layer of cylindrical epithelial cells an intermediate basal membrane and an external connective envelope provided with muscular fibers the contractions of which serve to eject the poison under pressure

COMPOSITION AND EFFECTS OF VENOM

Very little is known as to the real nature of the chemical constituents of spider venoms

From a physiopathologic point of view spider venoms may be systemized and grouped in the following principal categories (1) neurotropic (2) hemolytic and icterogenic and (3) dermotropic or necrotic

Virtually all spider venoms are neurotropic very few exceptions being known The species with most typically neurotoxic venom are *Ctenus nigriventer, Latrodectus mactans (L geometricus* and other species) among the Araneomorphae *Ctenia sauvagei Avicularia avicularia Phormictopus carcerides* among the Mygalomorphae

None is known to have an exclusively hemolytic or icterogenic venom The poison of *Latrodectus hasselti* (Araneomorpha) and that of *Grammostola acteon* (Mygalomorpha) are neurotoxic hemolytic and icterogenic while that of *Epeira diadema* (Aranemorpha) is neurotoxic and hemolytic but never icterogenic

The poison of *Lycosa raptoria* is typically dermotropic and necrotic while that of *Glyptocranium gasteracanthoides* is both necrotic and hemolytic (only slightly neurotoxic) that of *Araneus audax* is necrotic hemolytic and icterogenic and that of *Acanthoscurria sternalis* is slightly neurotropic and dermotropic

It is obvious that the manifestation of the effect of any of these venoms on the tissues under experimental conditions depends on the route of introduction and on the degree of receptivity of every laboratory animal Clinically however they cause destruction or lesions according to the prevailing cytotropism of the constituents

None of these constituents however should be confused with araneilysine a complex substance found in the body fluids of spiders particularly in fertilized females and their eggs and having hemolytic and neurotoxic properties of a different character

CLINICAL SYMPTOMS

In the light of the classification of the principal constituents of the venom the following types of araneism may be briefly indicated

Latrodectus mactans (L geometricus L lugubris L tredecimguttatus and *L menavodi)* red wheal at the bite (double puncture) pain swelling and numbness followed by fever depression shivering choreiform restlessness convulsions spasm and rigidity of the muscles of the abdominal wall and other regions vomiting hypothermia sexual excitation and anuria or death in severe cases *L hasselti* in addition to many of these symptoms causes internal hemorrhages and icterus

Ctenus nigriventer acute pain muscular spasms shivering cold perspiration salivation and lacrimation dysuria tachycardia and arterial hypotension sometimes terminating in death especially among children

Ctenzia sauvagei short depression narcosis and asthenia

Avicularia avicularia fever lipothymia and delirium

Grammostola acteon pain bloody swelling hemorrhages dyspnea paresis or paralysis salivation and occasionally icterus

Epeira diadema pain bloody swelling at the site of the bite and hemorrhages through mucous membranes hyperthermia and nervous depression

Lycosa raptoria extensive edema phlyctenules destruction of the derma at the site of the bite followed by sloughing of the affected tissue and by an irregular scar

Glyptocranium gasteracanthoides red wheal and papule phlegmonous edema phlyctenules sloughing of the skin and deep scar, depression tachycardia and dyspnea hematuria sometimes anuria

Araneus audax bloody edema phlyctenules sloughing of the skin and scar lymphadenitis headache fever tachycardia and dyspnea congestion of the bronchial gastric and intestinal mucosa icterus and oliguria



Fig 436 —Scar left on the skin of a child bitten by a true spider Aranomorpha (*Lycosa raptoria*) having necrotic venom

TREATMENT OF ARANEISM

The treatment of araneism is based on nonspecific and specific means

Nonspecific Means

Nonspecific means consist of symptomatic medication to follow the clinical evolution of every particular case Against the pain and local swelling warm dressings with concentrated solution of magnesium sulfate will bring some relief In some cases an intravenous injection of 5 or 10 c c of 10 per cent calcium gluconate solution is indicated Cardiotonics and general stimu

lants are advised against depression lipothymia and arterial hypotension Liver extract and blood transfusion will be effective in cases with marked hemolysis Injection of atropine to block the vagus followed by neostigmine to cause muscular relaxation is capable of counteracting cramps or spasms as observed in some serious cases of araneism caused for instance by *L mactans*

Specific Means

Since the death rate in araneism is relatively high in children (and light weight animals) and inasmuch as no really effective measure has yet been devised to exterminate spiders that infest some districts a few laboratories have attempted to prepare antivenins specific for certain forms of Araneida known to be either deadly or extremely pernicious

In this connection the Instituto Butantan has been preparing for the last 20 years 3 types of antivenin (1) anti ctenico for *Ctenus nigriventer,* (2) anti lycosico for *Lycosa raptoria* and (3) anti ctenolycosico for both of these species Sheep are preferred in immunization against these venoms Intradermal inoculations are made with Lycosa venom and subcutaneous injections with the Ctenus venom Titrations of both sera are carried out on rabbits Clinically lycosic antivenin must be injected around the site of the bite

In the United States the Antivenin Institute of America has prepared a specific antivenin to counteract the poisoning caused by the black widow spider *(Latrodectus mactans)*

More recently Pirossky Sampayo and Franceschi (1942) claimed to have prepared a very potent serum against *Latrodectus mactans* venom Since they used as an antigen the extract of whole cephalothoraxes of spiders in which araneilysine might be present it is hoped that other investigators will experiment farther in this matter In this case horses were used for the immunization and the serum was said to have been partially purified by peptic digestion or by sodium sulfate precipitation

The principle of specificity must be strictly adhered to in the serum treatment of cases of araneism

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CHAPTER 57

SNAKE VENENATION (OPHIDISM)

Afranio do Amaral

INTRODUCTION

Venomous animals are those whose toxic secretion, elaborated in a state of health, will cause disturbances in their victim only when they are pressed, squeezed, or swallowed by other species In this group are included the toads and certain fishes

Veniferous animals are those whose toxic secretion, elaborated in a state of health, will cause disturbances in their victim when that secretion is communicated to other species through biting, stabbing, or stinging In this group are included certain snakes, 2 lizards, a few fishes, the scorpions, the spiders, and the centipedes, besides some insects such as the wasps and the bees They can venenate either while attacking their prey and their enemies or while defending themselves from the attacks of other animals

CAUSAL AGENTS· SNAKES

Serpents are divided into the following families as recognized by the majority of the modern herpetologists

Typhlopidae Gunther, Leptotyphlopidae Stejneger, Boidae Boulenger, Anilidas Stejneger, Uropeltidae Gray, Xenopeltidae Cope, Colubridae Amaral (with two series of species recognizable through their tooth formation aglyphodont and opisthoglyphodont), Elapidae Gunther and Hydrophidae Smith (both of which form the third series of species *recognizable through their tooth formation proteroglyphodont)*, *Viperidae Bonaparte*, and Crotalidae Gray (both of which constiute the fourth series of species recognizable through their tooth formation solenotodont*)

Neither the aglyphodont nor the opisthoglyphodont series are of medical importance, since the representatives of the former do not bear any grooved tooth or fang wherewith they could inoculate their venom, while the representatives of the latter bear grooved teeth or fangs which however, are situated posteriorly in their mouth, thus being in an improper position to bite

The proteroglyphodont and the solenotodont series correspond to many species spread throughout the world, all of which not only secrete a toxic saliva, but also are apt to inject it by means of their grooved or hollow fangs on piercing the tissues of their prey or enemies Moreover, the fangs of both the proteroglyphodont and the solenotodont ophidians are situated anteriorly in their mouth, thus being in a position favorable both to biting and to stabbing their victims

Proteroglyphodonts.—Serpents belonging to this series are provided with small fangs longitudinally grooved and situated one on each side in the upper and front part of the mouth Each fang is firmly implanted in the anterior portion of the shortened maxilla, and this is closely articulated with the other bones of the skull It is also devoid of any direct motion so that the snake must hold on to the prey or victim to inject the venom into its tissues

*Or solenoglyphodont

The proteroglyphodont snakes are divided into 2 groups sea species and land species The former, represented by the Hydrophiidae, are found in the Pacific and Indian Oceans, only one species living in fresh water This is *Hydrophis semperi* which is confined to a lake in Luzon, Philippine Islands The remaining species, numbering about 90 at present, are encountered in deep water or near the shore (occasionally on land but never far from the seashore) all through the Indo Burmese region, near the Malayan Archipelago down to the Philippine Islands, along the coast of China and extending as far south as the Australian region (beyond New Guinea, Celebes, and Polynesia), and as far East as the west coast of Mexico, Central America, Panama, Colombia, and Ecuador

In their native habitat sea serpents are rather tame They are rapid swimmers, but on land they become virtually helpless, with the exception of one species, *Laticauda colubrina* Specimens of these have been found in a fishing village in Singapore among the poles supporting the houses which are built out over the water, whence they dip into the sea whenever they are hungry and return to their haunting grounds by climbing the poles as soon as they have fed

Although the majority of the sea snakes seldom exceed 1,200 mm (4 ft) in length, a few species are known to attain much larger size, as, for instance, *Hydrophis spiralis* and *Hydrophis cyanocinctus*—both of the Indo Burmese region—reach lengths of 2,700 mm or more (over 9 ft) and 1,800 mm or more (6 ft), respectively The black and yellow sea serpent, *Pelamis platurus*, is the species that has been captured sometimes along the west coast of the Americas and even in Gatun Lake, Panama

All sea snakes are provided with a laterally compressed, paddle like tail which facilitates swimming They feed on fishes and eels, whose movements they are able quickly to neutralize and whose respiration they stop through the action of their venom, which is highly neurotoxic, particularly in the Hoogli pattee *(Enhydrina schistosa)*, so common in the Indian Ocean

The latter group of the proteroglyphodont snakes, represented by the Elapidae all of which live on land, may be met all over the world except in the northern districts of the holarctic region Its members constitute by far the greater part of the ophiological fauna of Australia, where the following species deserve special mention, since they are all provided with very active venom the copperhead *(Denisonia superba)*, the tiger snake *(Notechis scutatus)*, and the death adder *(Acanthophis antarcticus)*, besides the brown snake *(Demansia textilis)* and the black snake *(Pseudechis porphyriacus)*

Among the representatives of this group may be cited the following species

1 The king cobra *(Naja hannah)* which has been aptly called the star serpent of the Indo Malayan region It is really not only the world s largest venomous snake, since it may reach the length of 5,400 mm (18 ft.) but it is also the most lethal of all reptiles in view of the extremely great amount of powerful venom it is likely to secrete It may be said to be the most dangerous of all living wild creatures Besides the high toxicity of its saliva, this snake is almost unique in being always active and inclined to attack. It is found in Tadjikistan, India, Burma, China, Indo China, Siam, Malaya, and the Philippines

2 The cobra de capello or spectacled cobra *(Naja naja)*, also found all over the range of the preceding species It never grows so large, average specimens measuring 1,800 mm (6 ft) It is responsible for the highest toll of lives taken every year by serpents anywhere in the world In India alone some 20 000 human beings (not counting innumerable animals both small and large) are known to be victimized annually by the cobra

3 The kraits, of which the common krait *(Bungarus candidus)*, the banded krait *(B fasciatus)*, the karawala or ringed krait *(B ceylonicus)* and the yellow headed krait *(B flaviceps)* are the most widespread and dangerous They are encountered in Southeastern Asia, Malaya, and the East Indies

4 The asp, or East African cobra *(Naja haje)*, so common from North Africa through Egypt to Natal that every skillful "snake charmer" uses it in his shows to dupe the tourist for gain

5 The spitting cobra *(Naja nigricollis)*, which has the widest range of all poisonous snakes in Africa, occurring from the Egypt Sudanese region southwestwardly to Angola and Transvaal It is also one of the most vicious and dangerous ophidians of the world Ditmars wrote ' The term 'spitting' does not correctly indicate the manner of ejecting the poison,

as the performance is accomplished with the jaws slightly parted and the venom comes directly from the openings at the tips of the fangs "

6 The black cobra *(Naja melanoleuca)*, which is the second largest of the African Elapidae, being second only to the Indo Malayan king cobra *(N hannah)* and the common mamba *(Dendraspis angusticeps)* It reaches 2,400 mm (8 ft) in length and is found throughout the tropical section of Africa, from Guinea and Uganda to the Shiré Valley

7 The South African cobra *(Naja flava)*, which is found from the Cape Colony up to the southern section of Tanganyika

8 The ringhals *(Sepedon haemachates)*, distributed all through South Africa It is also able to spit its venom, hence the name "spoewslang," which was applied to it by the Boers

9 The mambas, scattered through the tropical and subtropical sections of Africa They are all slender and arboreal, bearing a sort of protective coloration, which renders them inconspicuous and even unnoticeable in their natural habitat among leaves and branches in forests The black mamba, considered as the dark chromatic phase borne by adult specimens of the commonest species *(Dendraspis angusticeps)*, has been found as long as 3,600 mm (12 ft)

10 The coral snakes, genus Micrurus there are 2 species in the United States, namely, the harlequin or bead snake *(M fulvius)* of the Southeast and the Sonoran coral snake *(M euryxanthus)* of the Southwest

Several species, besides the 2 just mentioned, also occur in Mexico and Central America, the principal being *M affinis*, *M diastema*, *M elegans*, *M mipartitus*, and *M nigrocinctus* Throughout their range they are all popularly known as "coralillas" In South America, besides *M mipartitus* which occurs from Nicaragua southwardly to Venezuela and Peru, over 20 species are recognized, the most important are *M ancoralis*, *M balzani*, *M corallinus*, *M decoratus*, *M dissoleucus*, *M filiformis*, *M hemprichii*, *M langsdorffi*, *M lemniscatus*, *M narduccii*, *M peruvianus*, *M psyches*, *M spixii*, *M surinamensis*, *M transandinus*, and *M tschudii* These forms are also called "coralillas" throughout the Spanish American countries and "corais" in Brazil They secrete very little venom, the toxicity of which, however, is very great Fortunately, they are provided with rather minute fangs Their fangs are not movable, this is the primary reason why their bite is relatively rare The second reason is that the members of this group are quite tame when unmolested The third reason lies in that they must first close the mouth and hold on tightly to the victim in order to inject the venom into its tissues

Solenotodonts*—The ophidians included in this series are provided with very large fangs, hollow, like a hypodermic needle or a tube, with one "active" fang situated on each side, in the front upper part of the mouth These fangs are quite movable, since the short maxillary bones in which they are firmly implanted are rather loosely attached to the skull and very closely connected with powerful muscles, which is different from the structure of the Proteroglyphodonts

The solenotodont snakes are divided into 2 groups the pit vipers and the pitless vipers, according to the presence or absence of a pit or supplemental hole in the snout, placed between the nostril and the eye, and below their level All solenotodont ophidians encountered in the Americas (Western World) are pit vipers, while all those living in Europe and Africa are pitless vipers, those found in Asia, Malay Peninsula, and the East Indies belonging to either group

A Of the pit vipers about 100 species are recognized at present These are combined into the 6 genera which constitute the family Crotalidae

1 Of the genus Crotalus, the following are the most important species living in North America (Canada, United States, and Mexico) *C adamanteus*, the diamond black rattler of the southeastern states, *C atrox*, the Texas rattler of the southwestern states and New Mexico, *C cerastes*, the sidewinder of the extreme southwest, lower California, and northwest Mexico, *C enyo*, of lower California, *C exsul*, of Cerros Island (lower California), *C horridus*, the timber rattler of the eastern and central states, *C lepidus*, of Texas, Arizona, and north central Mexico, *C lucasensis*, of southern lower California, *C mitchellii*, the bleached

*Or solenoglyphodonts

rattler of Arizona, California, lower California, and islands, *C molossus*, of the extreme southwest and north central Mexico, *C polystictus*, of north central Mexico, *C ruber*, the red rattler, of southern California, lower California, and islands, *C scutulatus*, of the South western States and the Mexican plateau, *C stejnegeri*, of west central Mexico, *C terrificus*, the dog faced rattler, with 2 races, respectively, in west central Mexico and in southeast Mexico whence it has spread into Central America, *C tigris*, the tiger rattler of the deserts of Arizona and northwest Mexico, *C tortugensis* of Tortuga Island (lower California), *C triseriatus*, of southeast Arizona and Mexico, *C viridis*, the prairie rattler, of the Great Plains and the western states, from southern Canada to northwest Mexico and lower California, *C willardi* of southern Arizona and northwest Mexico

Of this genus only one form occurs in Central America This is *C terrificus durissus* which has spread from southeast Mexico and extends southwardly to Colombia and neighboring Venezuela

Throughout South America this genus is represented by the form *C terrificus terrificus*, which seems to have intergraded with the preceding race in some sections of Venezuela and Colombia Rattlers have not been reported from Chile and transandean Peru and Ecuador Throughout the Spanish American countries the rattlesnake is called "vibora de cascabel" or simply "cascabel," while in Brazil, among Portuguese Americans, it is known as "cascavel" and also "boiquira," and "maracaboia" among the Indians

2 Of the genus Sistrurus, which is typically North American, only 3 rather small or dwarfed species are recognized, to wit *S catenatus*, the "massasauga" of the prairies of southeast Canada, eastern, central, and west central United States and northeast Mexico, *S miliarius*, the ground rattler of the south central and western States, *S ravus* of New Mexico

3 The genus Agkistrodon is represented both in the Eastern and the Western Worlds by several species *rhodostoma* in Siam, Malaya, and East Indies, *hypnale* in Ceylon and India, *himalayanus* in the Himalayan range from 1,500 m to 3,000 m, *halys* in southwest Siberia and the Caspian Sea district, *blomhoffii* and *intermedius* in Siberia, China, Mongolia, and

and Zolcuate) in southern Mexico down to Guatemala and Honduras Both *piscivorus* and *bilineatus* may be found in marshes and streams

4 The Oriental genus *Trimeresurus* is made up of some 20 species of which the following deserve mention *cantoris* from the Andaman and Nicobar Islands, *flavomaculatus* from the Philippines, *flavoviridis* or habu, from Loo Choo Islands, Japan, *gramineus* or green, tree (sometimes bamboo) pit viper, the most widespread of the Eastern forms, since its range extends from India and Malay to southwest Oceania, *monticola* or spotted pit viper from the Himalayas (600 m to 2,400 m) to Burma and Sumatra, *mucrosquamatus* from Formosa, *purpureomaculatus* or Grey's pit viper, from India to Burma, Sumatra, and Andaman and Nicobar Islands, *sumatranus* from Malay to Borneo, *wagleri* from the Malayan Peninsula and Archipelago

5 The Occidental genus Bothrops, well distributed over the American tropical section, where it is represented by some 40 species, may be divided into 3 groups (1) land snakes, (2) arboreal snakes with nonprehensile tail, (3) arboreal snakes with prehensile tail.

Among the land living species of Bothrops the following deserve consideration *alternata*, the "urutu" of Brazil, "vibora de la Cruz" of Paraguay, Uruguay, and Argentina, *alticola* in the Andean section of Ecuador, *ammodytoides*, the "yarará ñata" of Argentina, *andiana* in F Peru, *atrox*, the "nauyaca" or "tepotzo" of Mexico, the "barba amarilla" or "terciopelo" of Central America, the "tamagá" ("tommigoff") of Panama, the "cuaima" or "echis" (because of its dorsal X like markings) of Colombia, the "terciopelo" or "taya" of Venezuela, the "fer de lance" of Martinique, Santa Lucia, Tobago, and Trinidad Islands, the "terciopelo" or "yarará" of Bolivia, Paraguay, and Peru the "caissaca" of tropical Brazil, *cotiara*, the "cotiara" of Subtropical Brazil, the "koatiá" of Paraguay and north eastern Argentina, *erythromelas* in central Brazil, *godmani* in Guatemala and Honduras,

hyoprora in the Amazon valley (Brazil and Colombia), *iglesiasi* in northeast Brazil, *itapetiningae* in southeast Brazil, *jararaca,* the "jararaca" of south central Brazil, the "yararaca" of Paraguay, Uruguay, and Argentina, *jararacussu* the "jararacuçu" of Brazil the "yarara guazu" of Bolivia, Paraguay, and Argentina, *lansbergii*, the "chinga" of southern Mexico and Central America, the "patoquilla" of Colombía, the "deroya" of Venezuela, *lojana* in the highlands of Ecuador, *medusa,* the "viejita" of Venezuela, *melanura* in southern Mexico, *microphthalma* in Peru and Ecuador, *nasuta,* the "tamagá" of Central America, the "hilvan" of Colombia and western Ecuador, *neglecta* in central Brazil, British Guiana, and Colombia, *neuwiedii* (including several races) the "jararaca pintada" of Brazil, the "yararaquita" of Paraguay, Bolivia, Uruguay, and Argentina, *nummifera* the "mano de metate" in Mexico, the "mano de piedra" or "timbó" of Honduras and Costa Rica, *ophryomegas* the "chatilla" of the Pacific slopes of Central America, *picta* in western Peru, *pirajai* in eastern Brazil, *pulchra* in the Andean section of Ecuador, and *xanthogrammus* in Ecuador and Colombia

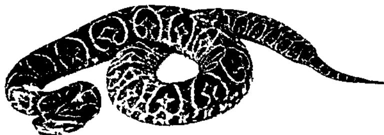


FIG 437 —*Bothrops alternata* the urutu of Brazil or vibora de la Cruz of Argentina and Uruguay



FIG 438 —*Bothrops atrox* the terciopelo of Spanish America fer de lance of Martinique or casissaca of Brazil

Among the arboreal snakes with nonprehensile tail the following are the only ones of any importance *castelnaudi,* the "trepadeira" of northwest Brazil, the "rabo de ratón" of eastern Peru and Ecuador, the "macabrel" of southeast Colombia, and *insularis,* the "jararaca ilhoa" of the Queimada Grande Island (off the southeastern coast of Brazil)

Among the arboreal snakes with prehensile tail, the following may be cited *bicolor* in Guatemala, *bilineata,* the "sucurucu de patioba" or "Oricana" of eastern and central Brazil, the "vibora verde" of eastern Bolivia, Peru, and Ecuador, *lateralis,* the "lora" of Costa Rica, *monticelli* the "rabo de chucha" of western Panama, Colombia and Ecuador, *nigroviridis,* the "vibora de árbol" of Costa Rica and Guatemala, *oligolepis* in the Andean section of Peru, *peruviana* in southeastern Peru, *schlegelii,* the "bocaracá" of Honduras and Costa Rica, the "toboba depestaña" of western Panama, Colombia, and Ecuador, and *undulata* in southern and western Mexico

6 The genus Lachesis is represented by but one species, that is, *muta*, the dreadful bushmaster of Trinidad Island, the "verrugosa" of Costa Rica, Panama, and Colombia, the 'mapanare' or "guayacan" of Venezuela, the "chuchupe" of the Peruvian Amazon valley, the "surucucu de fogo" or "surucucu pico de jaca" or "surucutinga" of tropical Brazil

B Of the pitless vipers there are seven genera including over 30 species which are spread throughout Europe, southern and western Asia (and Malay), and particularly Africa, whence the whole group, the Viperidae family, appears to have sprung

1 In Europe, therefore, outside of the tropical or subtropical zones, only one rather *unimportant genus, Vipera, has been found It holds 7 small species (including V berus, the* "kreuzotter" of Germany), of which 5 also occur either in Africa or in Asia

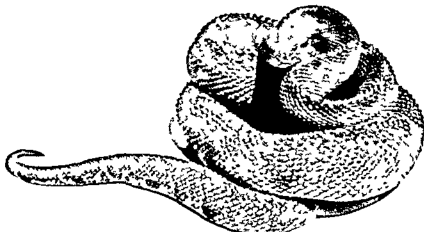


Fig 439—*Lachesis muta* bushmaster or surucuçu the largest pit viper and the most vicious snake of the American tropics

2 In Asia and Malay the following forms are known (besides 5 small species of Vipera)

(a) *Azemiops feae*, the "fea's" viper of Upper Burma

(b) *Pseudocerastes persica*, the "horned eye" viper of Persia

(c) *Vipera russellii*, the "daboia" or "tic polonga" of India, where it nearly rivals the spectacled cobra in taking yearly a high toll of human life, the largest and the truly deadly representative of the genus, it ranges from India and Ceylon through Malay to the East Indies

3 In Africa, which seems to be their paradise, vipers are represented by heavy terrestrial forms, light sand burrowing forms, slender arboreal forms, and large aquatic forms They make up 7 genera in all, with the following conspicuous forms (besides *Vipera superciliaris* of the coastal area of Moçambique and 2 more species of the genus Vipera that have spread to Europe or Asia)

(a) Genus Atractaspis, with about 12 burrowing species, all of which are provided with so extremely developed fangs as to defeat virtually their purpose, the most important ones (*bibronii, irregularis* and *rostrata*) occur throughout the tropical and subtropical districts

(b) Genus Causus, with the dreaded species *rhombeatus* (excluding other smaller ones), the night adder of South Africa, where it lurks in rubbish heaps, which increases its chances of biting human beings

(c) Genus Atheris, with 3 species, of which *chlorechis* lives in Liberia and *squamiger* in Angola, both being called "bush vipers"

(d) Genus Bitis, with several species, of which the most venomous are *gabonica* the gaboon viper, "the world's most frightful looking creature," spread across tropical Africa from coast to coast *nasicornis*, the rhinoceros viper or river jack of central West Africa, where it is found along streams, *arietans*, the puff adder, distributed from north central Africa to the Suez Canal zone, thence down to South Africa, *caudalis*, the Angola viper, and *atropos* (the Berg viper), *cornuta* (the horned viper), and *inornata* (the Cape viper) in South Africa

4 In Africa and in Asia simultaneously are encountered the following forms

(a) Genus Cerastes of sand vipers, of which *vipera* ranges from Algeria to Egypt and *cornutus* the horned sand viper, extends from northeast Africa to Arabia and Palestine

(b) Genus Echis of desert living forms, of which *coloratus* inhabits Arabia, Palestine, and Socotra, and *carinatus*, the deadly "efa" of Egypt or "phoorsa" of India may be encountered throughout the sandy districts of North Africa, Arabia, Persia, and India

Habits and Behavior of Venomous Snakes

While aglyphodont, opisthoglyphodont, and proteroglyphodont ophidians like the representatives of more primitive groups such as the Boidae, are as a rule quick in their movements, vipers are rather sluggish The forward motion of ordinary vipers, adders, and rattlers results from successive movements of the ribs, the tips of which lie just beneath the skin of the belly and flanks Arboreal vipers make a dextrous use of the tail by coiling it in a spring like manner around any branch or bough

A correctly aimed strike and a progressively strong constriction are employed by the nonveneniferous forms or aglyphodonts in order not to miss the opportunity of feeding and thereby of surviving Opisthoglyphodont species however being provided with back fangs or grooved teeth first seize their prey, then bring these teeth into action through repeated forward and sideward motions of the maxillae over the victim's body, whereupon they inject their venomous saliva into its tissues This excretion which is neurotoxic, paralyzes the muscles of the captured animal, making reaction impossible

Coral snakes are tame and live a secretive life They usually do not bite unless hard pressed by one unaware of their venomous nature

Regarding the Western World pit vipers particularly, the copperhead (*Aghistrodon mokeson*) is a rather vicious creature which gives no warning of its presence while in the open It moves quite suddenly and begins to strike in any direction whatsoever

The cottonmouth moccasin (*Aghistrodon piscivorus*) attacks everything that happens to move about it Its custom is to first open the mouth widely and then to strike in any direction whence it perceives danger

There seems to be some variation in temperament among rattlers

I have often observed that most rattlesnakes, when excited and getting ready to strike, coil up in such a way as to leave the head and the anterior third of the body raised quite high, forming angular loops with the hind part

of the body and tail As a rule this attitude brings the left side of the rattler's body inside of the coil, the neck region being doubled in an "S" shaped loop The loop is just what permits the snake to thrust the head forward In some cases, as often happens with the Texas rattler when it is very angry, it gradu

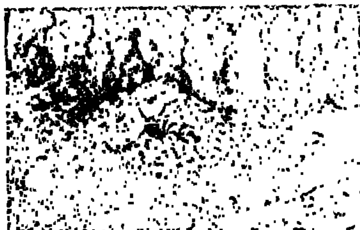


Fig 440 — A rattler (*Crotalus viridis*) getting ready to strike

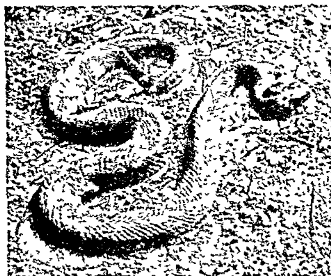


Fig 441 —Desert diamond rattl snake *Crotalus atrox* (Baird and Girard) (Photograph National Park Service) (From Merck Report, July 1946 from article by Stahnke Herbert L. Some poisonous animals of the United States by permission of the author and publisher)

ally raises the head well up in the air, 10 to 15 inches or more from the ground, according to its size Under these circumstances it does not strike upward, but sideways or downward However, when it is lying coiled, its head resting

somewhere on its body, it can strike almost vertically upward, as the thrust oftentimes forms an angle of nearly 70° with the underlying ground

Quite comparable to the behavior of the subtropical forms, both at rest and on striking is that of the typically tropical rattlesnake, the "cascavel" or 'boiquira," *Crotalus terrificus,* with the difference only that the latter very seldom makes any hissing sound either before or after the blow

The comportment of the dreaded bushmaster, *Lachesis muta,* is indeed unique This snake lives in holes in the ground or in fallen or decayed trees and while in the open and at bay, it coils up but, quite contrary to the usual habits of vipers it attacks and comes after anyone who passes within striking distance It may be explained that the bushmaster, or "surucucu de fogo" is the largest member of the solenotodonts, since it reaches a length of 3 600 mm (about 12 ft)

Poison Apparatus

The venom apparatus, having attained its maximum development among the solenotodont snakes consists of a gland, a duct and one or more fangs located on each side of the head The venom is the secretion of the external supralabial gland of the ophidians, which is found below and behind the orbit From the physiologic and biochemical standpoints the venom acts as a sort of saliva as such it serves both to facilitate the swallowing of the prey and to initiate the gradual digestion of the tissues of the prey by the combined action of several principles or enzymes which enter into its composition

Among the solenotodont ophidians the South American "jararacucu' *(Bothrops jararacussu)* and "urutu" *(Bothrops alternata),* and the North American diamond back rattler *(Crotalus adamanteus)* have the largest glands while the bushmaster *(Lachesis muta)* and the African *Atractaspis bibronii, A irregularis,* and other congeneric species possess the longest fangs Among the proteroglyphodonts the white striped coral snake *(Doliophis bivirgatus)* from Burma Malay, and the East Indies bears the largest glands, which extend along each side of the body for about ⅓ of its length, gradually becoming thick or globose and terminating in front of the heart Among the solenotodonts of the European African region, the South African death adder *Causus rhombeatus* and other congeneric species show a similarly aberrant glandular development The longest fangs among proteroglyphodont forms are found in the Abyssinian *Dendraspis antinorii* and other African mambas

Poison Inoculation

Inoculation of venom is accomplished by the synchronized action of several muscles all attached to the skull bones The bones most directly concerned with this action are divided into 2 groups each group making up the arm of a lever, the axis of which is represented by the joint of the squamosal with the quadrate Contraction of the muscles pulling from the rear and lower arm of that lever, assisted by the relaxation of the opposite group of muscles causes the closing of the mouth, and the lowering and retraction of the fangs, while contraction of the muscles pulling from the front and upper

group of muscles aided by the relaxation of the opposite group of muscles provokes the opening of the mouth and the raising and projection of the fangs

Moreover this combined muscular action occurring at the very moment the strike takes place is responsible for the instant and wide opening of the mouth up to an angle of 150 degrees or more and the compression of the glands thereby forcing the venom through the duct and fangs and into the victim's tissues At the end of the stroke the fangs are withdrawn from the victim s tissues (the whole action takes but a few seconds) whereupon the mouth closes again and the fangs are pulled back and return to their resting position hiding under the palatine membrane

SNAKE VENOMS

Volume of Venom

The amount of the venom secreted varies according to the species and in general is proportional to the size of the snake although there are exceptions to this rule sea snakes (Hydrophidae) secrete very little venom in relation to their size the neotropical rattler *Crotalus terrificus* secretes less and less poison as it grows older medium aged individuals yielding the largest volume

Captivity also exerts a noticeable influence on the secreting activity of the venom glands retarding or even inhibiting it through secondary infections

In the temperate zone serpents have been found to be quantitatively more poisonous immediately following the hibernation period Such is the case for instance with both the diamond back rattler *(Crotalus adamanteus)* and the Texas rattler *(C atrox)* specimens of which were found by Stadelman (1929) to produce as much as 1 000 mg (1 Gm) dried weight at a single extraction

In exceptional instances it has been proved that some solenotodont snakes such as the bushmaster *(Lachesis muta)* the diamond back rattler *(Crotalus adamanteus)* the Texas rattler *(C atrox)* and the fer de lance *(Bothrops atrox)* may yield much larger amounts of venom if carefully captured and kept undisturbed

Chemical Nature of Venom

A venom is a complex of many toxic principles and antigenic substances which have especial tropism for different animal tissues It is likely that these principles and substances which must have gradually appeared in the saliva as the result of natural selection are specific weapons whereto ophidians being limbless and otherwise defenseless have recourse in their struggle for life

Venoms are commonly classified with the proteins because of their most important reactions and physicochemical affinities They lose their toxicity when treated in vitro by such reagents as silver nitrate sodium and potassium hydroxide gold chloride potassium permanganate formaldehyde and others They also become atoxic when heated but at widely different temperatures They are not modified by glycerin which therefore serves as the usual means

of preservation in the laboratory Venoms are also stable when desiccated and kept away from air humidity heat and light

Until recently very little was known concerning the chemical composition and the real nature of the toxic principles of the venom

Micheel and collaborators Bode Jung Dietrich and Bischoff (1936 1939) working with the venom of both the Indian and the African cobras found that the neurotoxic constituent is not only protein in character but seems to contain a thiolactonic group

Only recently however has the real chemical nature of snake venom been disclosed Slotta and associates working under my direction at the Instituto Butantan in S o Paulo Brazil (1936 1938) have confirmed the findings of Micheel and associates and are inclined to ascribe to the presence of 5 to 7 active atoms of sulfur an important binding role in the large protein molecule of neurotoxin giving it a peculiar specificity Moreover they have separated from the venin of the cascavel *(Crotalus terrificus)* an active substance which is responsible for its marked neurotoxicity and perhaps for its slight hemolytic power as well This substance which they have named crotoxin " is the first animal proteinous venin ever to be isolated in purely crystalline form

The highly complex formula of crotoxin" may be briefly written as $C_{336}H_{2096}O_{4\,0}N_{372}S_4$ Its molecular weight is approximately 30 500 in the light of ultracentrifuge determinations carried out by Svedberg and collaborator Gralen (1938)

Crotoxin which is also a homogeneous substance has proved in the course of electrophoresis experiments performed by Li and Fraenkel Conrat to have the value of $d\mu/dpH_0$ as its isoelectric point

Coagulin is the second substance that has been found in viper venom It is connected with the mechanism of blood coagulation and proteolysis as exerted by venins It is soluble in distilled water while crotoxin is not According to the old classification of proteins into globulins and albumins coagulin is of an albuminoid character and crotoxin is globulinoid In therapeutics we have taken advantage of coagulin by employing it as hemostatic in various hemorrhagic conditions The coagulant principle of *B jararaca* venom has been called bothropotoxin by von Klobusitzky and Koenig my former assistants at the Instituto Butantan

VENENATION

Both the toxic and the antigenic principles of snake venom which are bound to the proteins are responsible for the severe symptoms as usually brought about by the bite They may be included in 4 biochemical categories of substances neurocytolysins or neurolysins hemocytolysins or hemolysins hemocoagulins and proteolysins all of which deserve special mention since they either affect the vital functions of the body or cause extensive destruction of the tissues

Neurolysins show an accented tropism for the cells of the neuraxis and
the autonomous system as well This explains why they have a systemic
effect and may disturb respiration circulation, tissue metabolism, eyesight,
perspiration and other important functions They are usually found in the
venom of the proterodonts, Elapidae and Hydrophiidae, and such soleno
todont forms as the neotropic cascavel *(Crotalus terrificus)*, the African
night adder *(Causus rhombeatus)*, and the efa of Egypt or phoorsa of India
(Echis carinatus) In this type of ophiotoxicosis, death may be due either to
direct curarization or to arterial hypotension or even both combined

Hemolysins both for the red cells and for the leucocytes are responsible
not only for the aggravation of local symptoms brought about by the action of
proteolysins on tissue proteins and consisting of swelling and phlogosis in
general since the earlier stages, but also for the respiratory disturbances which
appear at the later phases of some types of venenation The effect of the
hemolysins seems to be related to the enzyme lecithinase, which is likely to set
free ... under the influence of certain venoms, lecithin thus liberated
is in... ... or lysocithin in contact with blood
that ... ...olysin, finally
... by alter
... ke of the
lysocithin will act on the bloo... hemolysins cause ...
ing the composition of the blood hemolysins cause the
tissues to drop They are abundant particularly in the venom of the spectacled
cobra *(Naja naja)* and the tic polonga *(Vipera russellii)*, the Texas rattler
(Crotalus atrox) the South American urutu *(Bothrops alternata)*, the neo
tropical fer de lance *(Bothrops atrox)*, and the water moccasin *(Agkistrodon
piscivorus)* to a certain extent

Hemocoagulins may have a variable effect on the blood Assuming that
blood coagulation is due to the action of a double enzyme system one, trypsin
like in character (and related to thrombokinase or cytozyme) which reacts on
prothrombin or serozyme to form thrombin, and another, papain like in char
acter (and related to fibrinogenase) which reacts on fibrinogen to form fibrin
Eagle (1937) has found that certain snake venoms behave likewise in this re
gard Therefore, some venoms will react with prothrombin to form thrombi
while others will react with fibrinogen to form fibrin In the former group a
... venoms of at least the following species fer de lance *(Bothro*
... among the solenotodonts, and tiger sna
... and
... r gro
... *Crota*
lemniscatus = *fronti...* ... *B jararaca* (both ...
are included *B atrox*, *B jararaca* ... Finally, there are some types
... and *C terrificus* These appear to destroy either
...
same ...
piscivorus, *Bitis arietans*, *Crota*...
... of some snake ...

Proteolysins are the phlogogenic constituents of some snake ve...
affect the site of the "bite" and act on the walls of the capillaries, causing

swelling, blood extravasation, necrosis, and ultimate mutilation They are found principally in the venom of the majority of the solenotodonts, the stab of which may become lethal either primarily, because of extensive destruction of tissues, or, secondarily, due to subsequent invasion by bacteria

Noteworthy Types of Ophiotoxicosis—Clinical Symptoms

The symptoms resulting from the "bite" or stab of the most dreadful species of serpents may be briefly summarized as follows

The American Coral Snakes *(Micrurus corallinus, fulvius, lemniscatus,* and others) —No local phenomena occur other than pain, which is usually quite intense General symptoms are rather severe and consist of depression and somnolence, trembling and convulsions, salivation and lacrimation In these cases death is due to collapse

The Indo Malayan or Spectacled Cobra *(Naja naja)* —Its venom produces an intense local burning sensation, some edema and congestion, prostration and somnolence, salivation, nausea and vomiting, cold perspiration, blood destruction with accelerated and thread like pulse, rapid respiration (tachypnea) at first, subsequently becoming weaker and slower Difficulty of speech appears, progressive interrupted muscular paralysis, hemorrhages at times through the mucous membranes If the dose of venin is not sufficient to cause definite paralysis, the patient will recover and the general symptoms disappear rather rapidly Otherwise the patient dies from respiratory paralysis, the heart action however continuing for a short time

Similar symptoms of toxicosis are caused by the venom of the hoogli pattee, the Indian sea snake *(Enhydrina schistosa)*, with the difference, however, that in this case the local reaction is not severe, hemorrhages are absent, and death occurs in the course of respiratory convulsions

The King Cobra or Hamadryad *(Naja hannah)* —The venom of this most awesome serpent, which is the largest poisonous species of the world, acts almost exactly like the venom of the spectacled cobra It kills by paralyzing the respiration as it acts on both the respiratory center and the terminations of the phrenic nerve It differs from that venom, however, in being very slightly hemolytic and in affecting the central nervous system rather quickly, due perhaps to its tropism for the nerves and to the enormous amount in which it is secreted For these reasons poisoning by the king cobra appears to be the most severe on record, death oftentimes taking place in less than an hour

The Common Krait *(Bungarus coeruleus)* —Intoxication due to the venom of this species is responsible for a great number of deaths in India alone This venenation manifests itself preferably on the nervous centers and especially on the respiratory center Breathing becomes difficult and stertorous There is no apparent local reaction The patient remains in a subconscious state until death

The Banded Krait *(Bungarus fasciatus)* —Death is the result of paralysis of the respiratory center This occurs after 2 or 3 days or, in some cases, after

a longer period—6 days or more—being preceded by anorexia and general depression loss of weight muscular weakness emaciation oliguria and other symptoms of slow toxicosis

The Black Mamba *(Dendraspis angusticeps)*—This is the most dreaded snake in Africa It causes a type of poisoning which resembles in many features that caused by the common krait

The Tic Polonga or Daboia *(Vipera russellii)*—Characteristic features are strong local reaction with development of ecchymoses and hemorrhages due to lack of blood coagulation There are also accentuated general phenomena consisting principally in a tendency to collapse, rapid and thread like pulse, nausea vomiting pupillary dilatation and loss of consciousness If the patient does not die immediately the local edema spreads rapidly Hemorrhages occur at the point of the "bite" or into the mucous membranes due to hemolysis hematuria and albuminuria appear followed by anemia and intense emaciation causing death In these cases no signs of intoxication of the central neuraxis are ever found.

The African Puff Adder *(Bitis arietans)*—Its venom like the daboia s provokes intense local reaction with edema extravasation of blood, infiltration hemorrhages and ecchymoses It is not hemocoagulant but it is proteolytic and slightly hemolytic Death as a rule supervenes either rapidly from blood suffusion through the mucous surfaces and into the brain tissues or slowly from progressive necrosis and gangrene a week or more after the "bite" has been inflicted

The Pit Vipers, Both American *(Bothrops alternata atrox jararaca, jararacussu nummifera* and others) **and Asiatic** *(Trimeresurus flavoviridis)*—Formidable reaction supervenes consisting in immediate edema which spreads rapidly, glandular swelling serosanguinolent subepidermic infiltration terrible pain ecchymosis and hemorrhage at the site of the "bite" Later because of the action of these venoms on the tissues in general and most particularly upon the proteins of the red cells and upon blood coagulation general symptoms follow consisting of parched throat thirst congestion and hemorrhages through the mucous membranes except in poisoning by the habu These hemorrhages which start through the mucosa of the eyes mouth nose, stomach intestines and bladder may occur even through the ears and the skin Albuminuria also appears Finally the patient becomes completely exhausted the body temperature falls and death ensues. Whenever death does not supervene then the gangrene of the tissues most affected progresses until complete mutilation is the final outcome of the venenation

In this group of venoms none has any manifest effect on the neuraxis or the autonomic nervous system except that of the jararacuçu *(B jararacussu)* which as a rule brings about impairment of the sight The venom of the habu *(T flavoviridis)* is also known to cause paralysis of the respiratory center Only exceptionally there may be observed paresis or even paralysis of the limbs in the course of envenoming by *B jararacussu* and *B jararaca*

The North American Rattlers *(Crotalus adamanteus horridus, ruber, viridis* and others) **and the Neotropical Bushmaster** *(Lachesis muta)*—Their

venoms cause local pain and hemorrhage and edema and discoloration of the "bitten" region, which gradually is rendered ecchymotic and covered with phlyctenules, gangrene may be the outcome In view of the rapid absorption of the venom constituents by nerves, blood, and lymph, general symptoms are apparent almost immediately, the most marked being extreme prostration, cold perspiration, nausea, vomiting, and sometimes diarrhea, weak and quickened pulse, and subsequently, dyspnea and repeated collapse, until death takes place with great agony

In this group of pit vipers the Texas rattler (*C atrox*, together with the water moccasin or *Agkistrodon piscivorus*) represents an exception Its venom is hemolytic but not hemocoagulant In vivo it acts like the venom of the daboia, causing no neurotoxicosis This peculiarity may explain the findings of Jackson and Githen (1931) as to the possibility of treating the poisoning caused in dogs by the Texas rattler by means of incisions and suction applied in the vicinity of the "bite"

The Neotropical Cascavel *(C terrificus)*—There is practically complete absence of local phenomena in the case of poisoning by this venom Impairment of the visual function, or even absolute blindness, may occur, lasting for a few minutes to several days, even after the patient has recovered through treatment or spontaneously In the later stages there is impairment or a true paralysis of both the general motion, particularly about the neck which acts as though it were broken, and the locomotion, then of the respiratory muscles, and finally death

Summary

We may conclude from these data that each venom causes its peculiar reaction, according to the amount of neurolytic, hemolytic, hemocoagulant, and proteolytic or other principles or enzymes contained therein, giving it specific character toxic and antigenic specificities Nevertheless there are certain similarities between the venoms, principally when the respective snakes belong to kindred species (eventually, to closely allied genera), in which case the active constituents of the venin are about the same, although their relative percentages vary from species to species

Death Rate

Contrary to the general belief and to certain stories spread by a great many travelers' books, veneniferous serpents are rather rare in tropical forested countries Although the number of species is fairly large, the density of the ophidic population—which is comparatively high in subtropical and temperate districts except in winter, when serpents go into hiding seeking protection from the cold weather—is relatively low in jungle sections In those places venomous reptiles meet with many forms of predatory animals which not only kill them for food but also compete advantageously with them by destroying the ordinary prey of snakes

The death rate caused by snake poisoning varies in the several regions according to the greater or lesser aggressiveness of the snake and the activity of the venom of the species found in each country It is known that an average

of about 30 000 deaths occur annually in India alone at present as a result of ophidic accidents of which the majority are caused by the spectacled cobra whereas there were but 14 fatal cases of venenation in Europe during the period 1883 1892 caused by the common viper and from 1898 to 1906 there was registered in the Okinawa Island an annual average of 225 3 persons venenated by the habu with a death rate of approximately 15 per cent

In Brazil the Instituto Butantan has been able to obtain reliable statistics of the accidents which have occurred in the State of Sao Paulo These statistics show the number of cases of snake bites to have been on an increase until the period 1906 to 1912 when they began to decrease following the increasing use of antivenins Prior to the general use of specific antivenins the death rate from ophiotoxicosis in that State seems to have been as high as 20 to 25 per cent of the cases This rate decreased very sharply to 6 to 8 per cent with the introduction of specific sera and has since gradually diminished to 3 or 4 per cent following the improvement introduced into the technic of antivenin preparation and application

In the light of these statistics it appears certain that it is impossible to lower the death rate from the present figures for the following reasons

1 Because both children and animals (especially dogs) contribute about 30 per cent of the total number of cases of snake poisoning

2 Because children and dogs having a low body weight receive relatively larger amounts of poison per kilogram which therefore acts in a greater concentration on their tissues snakes being unable to discriminate between a small and a large victim when they stab or bite The death rate of children and dogs is 3 7 and 10 4 per cent respectively of the cases treated with antivenins as against 2 5 per cent for adult persons

3 Because children usually do not properly report what has happened to them when they are found to suffer from snake poisoning and dogs are unable to report anything they are usually seen when their toxicosis is already in a very advanced stage

In the United States of America in the light of statistics assembled by the Antivenin Institute there are about 2 000 to 3 000 cases of snake "bite" every year the death rate varying from 10 per cent to 35 per cent This variation is related to the greater or lesser toxicity of the venom of the species prevalent in each section of the country

In regard to fatal bite accidents in other regions it is not possible to make even an approximate computation since there are no statistics on this subject
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toll of human lives taken yearly by serpents all over the world

PREVENTION OF OPHIOTOXICOSIS

Snake venenation with all its terrific consequences can be prevented in 2 ways first by preventing snake stabs second by applying specific treatment against the effects of the stab

Prevention of Snake Stabs

Various means have been developed for the prevention of snake stabs and they can be grouped into 2 principal types of measures individual protection and collective protection

Individual Protection—Since it is known that according to the different districts considered about 60 to 90 per cent of the stabs of venomous snakes are inflicted on the feet or legs it is simply a matter of common sense for one to wear boots and heavy leather leggins to achieve the necessary protection whenever one goes into a snake infested district

The stabs of the copperhead and of the timber rattler are sometimes inflicted on the hands because both these snakes live on ledges where they may be encountered in the path of a person trying to climb a rock and using his bare hands to help the ascension

The best means of personal protection against ophiotoxicosis consists of active immunization with anavenin that is detoxified venom (venom treated by formalin and heat) This type of vaccination is strictly specific against any venom against which one may seek protection It is achieved by a series of hypodermic injections using increasing doses from 0 2 to 2 or 5 c c of anavenin

Collective Protection—Collective protection is secured chiefly through extermination of venomous ophidians This may be done by several methods (1) by systematically killing veneniferous snakes (2) by capturing those snakes alive (3) by raising animals that feed on snakes

1 For nearly half a century a few countries have attempted to get rid of snakes by systematically killing them In India the British officers have sought to diminish snake toxicosis by encouraging the killing of snakes and paying a fixed bounty for each head brought in Despite all efforts in this direction the British authorities have not been very successful in their humanitarian campaign after the work of several years the death rate from snake bites in India seems not only not to have been reduced but rather increased One of the reasons for this failure in India is the superstitions of the Hindus who would rather die than kill snakes particularly the spectacled cobra because they believe that a deity hides behind the hood of its neck

As a matter of fact complete extermination of serpents seems to be impossible unless all traces of jungle forests rocks marshes and other snake sites are removed Moreover destruction of vipers can never be achieved in agricultural sections primarily because these snakes feed chiefly on rodents the number of which increases with the development of agriculture and secondarily because both snakes and rodents follow a very well known biologic law applicable to all animals (except of course those that follow birth control) the more they feed the more young they bear

2 Capturing live snakes is likely to become a much more successful method of combating viper stabs because by removing veneniferous serpents from their habitat we automatically remove one potential danger and also by keeping those snakes alive we can secure from them a supply of venin that may be used in the preparation of antivenins or antiophidic sera

One can capture live poisonous or more properly, veneniferous snakes by using a wire hook a leather lasso or even a forked stick made from a branch of a tree

3 Raising animals that feed on snakes is a method that never fully succeeds in practice A few of the Lesser Antilles have imported the mongoose *(Herpestes griseus)* from India with a view to exterminating the local vipers since it has long been known that among ophiophagous animals this mammal due to its quick sight and extraordinary agility rather than to any immunity whatsoever to venom can attack and kill poisonous serpents Unfortunately the mongoose although clever enough to escape being stabbed is perhaps more fond of poultry (and we could not blame him for his preference) than of snakes so that it has of late become a sort of nuisance to the countries that have imported it In Brazil a species of skunk *(Conepatus chilensis)* is known to feed on pit vipers being immune to their venom



Fig 442—The neotropical mussurana (*Pseudoboa cloelia* nonpoisonous) swallowing a pit viper (*Bothrops jararaca*)

The raising and protecting of serpents that kill other serpents (serpentivorous species) is a still less satisfactory method because of the difficulties involved Such species as the Brazilian mussurana *(Pseudoboa cloelia)* and the American black snake *(Coluber constrictor)* and king snake *(Lampropeltis getulus)* that have been known to feed on other serpents including pit vipers are of no value in practice because they usually try to find other perhaps less repugnant food In this respect it can be safely affirmed that whenever people have tried to break the rules of or change conditions in Nature the *results have not always been encouraging* Moreover most persons are still inclined to kill any serpent they encounter Correcting this inclination depends upon educational measures the adoption of which takes time

TREATMENT OF OPHIOTOXICOSIS

Therapeutic measures directed toward counteracting the effects of snake venoms on the tissues are divided into 2 categories nonspecific means and specific means

Nonspecific Means

Nonspecific means of counteracting the effects of snake venoms on the tissues consist of (1) ligature, (2) incision (3) suction

1 The ligature or tourniquet must be applied above the stab It should be made tight at first but must be partially released for a few seconds at 5 to 10 minute intervals to maintain the necessary circulation in the limb

2 In the majority of the types of ophiotoxicosis there is no particular advantage in making an incision nor in applying potassium permanganate in solution *or in crystals or in any of the other chemical agents commonly recommended* for this purpose In fact it is advisable to avoid any further mutilation or injury of the affected tissues especially because should the wound not be kept properly dressed until complete recovery tetanus or other secondary infections might set in and complicate the patient s condition In regard to potassium permanganate it has been shown that to have any effect on the venom this substance must be used in concentrations that are injurious to the tissues It has no effect in weak solution and in itself is toxic if used in too strong solution

3 Suction even when strong enough has many limitations since it is applicable only against the local type of venenation caused by such snakes as the Texas rattler *(Crotalus atrox)* the tic polonga or daboia *(Vipera russellii)* and the African puff adder *(Bitis arietans)* The venom of these species is hemolytic but not blood coagulant It causes a great local swelling and is absorbed mostly by the lymph vessels It forms *lysocithin* in contact with the extravasated blood and it is this substance and not diluted poison as has been claimed by some that is extractable by strong suction when applied to these restricted types of ophiotoxicosis

Above all the use of alcohol or any stimulant of this kind must be avoided These stimulants by strengthening the circulation may tend to help the absorption and distribution of the venom throughout the body Strychnine or caffeine however may be administered or a cup of hot coffee or tea given if symptoms of weakness and giddiness develop

Specific Means

Antivenins or antivenomous sera are the only specific means of neutralizing venins and arresting their harmful effects on the tissues

Calmette claimed that there is no specificity between antivenins and venoms He held that any antineurolytic serum could be applied to accidents issuing from whatever kind of neurolytic animal venom His theory however has proved to be untenable through studies carried out by Lamb (1904) Ishizaka (1907) Tidswell (1909) Noguchi (1909) Brazil (1909) Arthus (1911) Gomes (1920) Houssay and Negrete (1923) and do Amaral (1923)

At present we admit that for an antivenin to be really efficacious it must be produced in an animal immunized against the venom of the particular species of snake that has caused the accident or at least that of a more or

less related species This means that the principle of the specificity (and to a certain extent that of paraspecificity) of antitoxins applies to antivenomous sera

Specificity is due to the fact that a similar antigenic composition may be found only among venoms of serpents closely related to each other from a zoological standpoint Following this principle a number of laboratories have been engaged in the preparation of antivenins against the snakes prevalent in their countries or even elsewhere but unfortunately until recently not all had closely followed the improvements introduced into the technic of serum therapy Of the various laboratories that have in the past prepared or are still preparing on a large scale antivenins for curative purposes the following are outstanding Pasteur Institute (France and Indo China) polyvalent especially against the spectacled cobra (*Naja naja*) and the African vipers Institute for Infectious Diseases (Japan), monovalent against the habu Central Research Institute (Kasauli India) bivalent for the spectacled cobra and the daboia Haffkine Institute (India) bivalent for the spectacled cobra and the daboia and polyvalent (in a lyophilized condition) for the spectacled cobra the daboia the krait and the phoorsa Commonwealth Serum Laboratory (Australia) monovalent for the tiger snake Instituto Bacteriologico (Buenos Aires Argentina) bivalent for the cascavel and the vibora de la Cruz (*Bothrops alternata*) Similar organizations have of late become engaged in this line of work both in Mexico and in South Africa as well as in Austria and Yugoslavia so that specific antivenins are now available against the poisoning caused by the local serpents

The Instituto Butantan (Sao Paulo Brazil) in its many years of activity has prepared the following antivenins (1) monovalent *crotalico* for the neotropical cascavel (*Crotalus terrificus* (2) monovalent *botropico* for the South American jararaca (*Bothrops jararaca*) (3) monovalent for the neotropical bushmaster (*Lachesis muta*) (4) polyvalent *elapinco* for the South American corais (genus Micrurus) (5) polyvalent *botropico* for several of the South American rattleless pit vipers (6) polyvalent *ofidico* for both the cascavel and the rattleless pit vipers (genus Bothrops)

The Antivenin Institute of America (Glenolden Pennsylvania) has prepared 3 types of antivenin (1) Nearctic crotalidic for the North American rattlers the copperhead and the cottonmouth moccasin (2) Bothropic for the Central American fer de lance (3) Neotropic crotalic for the Central American rattler (*Crotalus terrificus durissus*)

Application of Antivenin —The following instructions must be adhered to

1 Should you not have the proper antivenin with you at the time of the accident proceed at once to the nearest place where this specific and proper medical attention can be obtained

Constriction of the limb must continue but care should be taken to release pressure at intervals of 5 or 10 minutes for about 1 minute at a time

2 Injections of antivenin may be made under the skin of the thigh or preferably on the side of the abdomen if applied by the victim himself or between the shoulders if administered by someone else

The hypodermic or intramuscular routes of injection may serve in the majority of the cases of ophiotoxicosis particularly in adults or in patients treated early Preference should be given to the intravenous route whenever the case is of a serious character

If the specific serum can be given at once or within the first hour or two after the stab or bite a portion of the syringe or ampule 5 c c for instance should be given by subcutaneous injection around the punctures left on the skin by the snake's fangs This tends to prevent destruction of the tissues particularly in those cases in which the bite happens to have been inflicted by the Texas rattler *(Crotalus atrox)* the daboia *(Vipera russellii)* or the puff adder *(Bitis arietans)*, the venoms of which are known to cause great local swelling and to be absorbed mostly by the lymph vessels In cases treated late however the local application of antivenin is probably of little avail

Dosage—The doses of antivenin should be proportional not only to the estimated quantity of venom inoculated by the serpent but also to the toxic activity of the poison and to the relative weight of the patient

Since in general the larger the snake is the greater the volume of venin it is able to inject it is advisable to give more than 1 dose (10 c c) of antivenin in the case of an accident caused by a large specimen Also a rather large dose of antivenin is necessary to counteract the effects of the ' bite of such snakes as the king cobra *(Naja hannah)* the spectacled cobra *(N naja)* the cascavel *(Crotalus terrificus)* the fer de lance *(Bothrops atrox)* the bush master *(Lachesis muta)* the daboia *(Vipera russellii)*, the jararacuçu *(B jararacussu)* the diamond back rattler *(C adamanteus)* the Texas rattler *(C atrox)* and the tiger snake *(Notechis scutatus)* the venoms of which either are highly toxic for the tissues of animals or are secreted in too large amounts for a person to resist

Finally since the toxicity of any venin is inversely proportional to the victim s body weight it is strongly recommended that 3 to 5 times as much antivenin be given to a child as to an adult Contrary to the statements of previous authors and specialists I have very definitely proved that the ratio between dosage and age of the person stabbed (approximately corresponding to his weight) is just the reverse of the usual dosage recommended in cases of bacterial infections The amount of venom injected is the same whether a child or an adult is stabbed since no serpent can discriminate between a small and a large victim

The smaller the patient the greater the need of the antivenin When there is reason to believe that the venom injected by the serpent was of unusually large quantity or when the symptoms develop quickly and in severe form as for instance in children it is advisable to give a second a third or even a fourth dose if indicated that is if the first has not caused the symptoms of venenation to subside

It sometimes happens that, after the first shock and reaction have passed, the patients will show marked improvement Some fatalities from snake venenation are plainly caused by an undue sense of security following the observation that most patients do well for the first 15 hours Even though the general symptoms may be mild, it is important to keep the patient under close observation for at least 24 hours or up to 1 month, as in the case of the neotropical cascavel due to the possibility of relapse within this period, and active treatment should be continued as long as the swelling is progressing Repeat the injections of antivenin every 1 or 2 hours if the swelling is increasing or if the patient's general condition is becoming worse The danger always lies more in undertreatment than in overtreatment.

It is most important to bear in mind, in late and severe cases, particularly in children or whenever profuse bleeding or symptoms of liver injury, low blood pressure and dehydration have appeared, that rapid relief may be secured from liberal doses of physiologic saline, given warm and slowly by the intravenous route, followed by glucose solution or Ringer sodium lactate *solution also injected warm and slowly into the vein Blood transfusion and* liver extract are effective in counteracting anemia following marked hemolysis

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CHAPTER 58

POISONING BY FISH AND OTHER ANIMALS

AFRANIO DO AMARAL

CENTIPEDES

The body is rather flat and segmented, each segment bearing a single pair of articulated legs, one leg on each side of every segment. The head is provided with a pair of antennae, a pair of small maxillary palpi and a pair of large, hollow, movable forcipulate fangs. Each fang encloses a venom gland, the secretion of which is ejected at the moment of the bite through an opening just behind the tip. Each gland is surrounded by a layer of muscular fibers which on contraction cause simultaneous adduction of the fangs and ejection of the venom; when these muscle fibers relax, the fang is abducted or brought to the resting position.

The venom facilitates catching small animals on which the centipedes feed, such as insects, lizards and spiders, by causing instant paralysis. It is a clear, homogeneous substance of acid reaction, but is secreted only in very minute amounts. Although no serious attempts have ever been made to analyze its chemical composition, it is known from observation that it causes a marked local reaction, consisting of an inflammatory wheal, pain and swelling, that immediately begins to spread centripetally, followed by local necrosis. If the amount of venom ejected at the bite is large enough relative to the weight of the prey, progressive paralysis ensues and the victim dies within a few minutes.

Painful as the bite may be to humans, it seems not to cause death. For this reason therapeutic measures are confined to the administration of sedatives and also intravenous injections of 5 to 10 c.c. of 10 per cent calcium gluconate solution and the local application of a warm dressing with a concentrated solution of magnesium sulfate.

WASPS AND BEES

Wasps

These insects, which are divided into many species with solitary as well as social living habits, feed mostly on other insects and spiders. In order to render their prey powerless, they poison it with the secretion produced by a double gland which they bear at the abdominal end. For this purpose they are provided with a long sting (especially powerful in workers and females) which, while resting, is hidden in a cavity between the openings of the digestive tract and of the sexual organs. One of the glands produces an acid secretion which is collected into a bulb or reservoir whence it passes to the

base of the sting while the other gland elaborates an alkaline secretion which passes directly to the base of the sting Both glands are surrounded by a muscular wall the contraction of which causes ejection of the secretions these being first collected into a small chamber or vesicle communicating with the sting canal The opening and closing of the orifice of the acid gland are controlled by two muscles of opposing functions so that the wasp can regulate at will the composition of the venom that flows into the sting chamber Therefore the venom represents either the alkaline secretion alone or a mixture of the two types of secretion the acid being more toxic than the other

The sting canal is occupied by a pair of darts the alternate propulsion and retrocession of which facilitates the flow of venom as they work like pistons in a pump Since the tip of each dart is rough and barbed the sting sometimes becomes stuck or entangled in the skin of the victim When this occurs the wasp cannot survive long

Although no experimental work has been done to ascertain the chemical composition of the venom of wasps it seems in general to contain a neurotoxin a proteolysin and a hemolysin The presence of these substances is responsible for the following symptoms following the sting

Local Symptoms—Local symptoms are a red wheal pain and burning sensation spreading edema hemorrhage under the skin most directly affected sometimes necrosis

General Symptoms—General symptoms are nausea vomiting lipothymy and syncope hypothermia arterial hypotension and bradycardia sometimes urticaria and exceptionally death particularly when the patient has suffered simultaneous stinging by several wasps cramps and spasms may appear

Since we do not know as yet of any specific treatment for this poisoning we must confine ourselves to giving the patient some heart stimulants epinephrine being particularly valuable narcotics (morphine opium) are helpful warm dressings with warm concentrated solution of magnesium sulfate may relieve the local pain and edema Atropine and neostigmine to combat spasms should be tried

Bees

Bees like the wasps are provided with a complex stinging apparatus particularly well developed and powerful in the queen and workers the males being devoid of venomousness Even the females however do not bear a sting in all of the families the American representatives of the Apidae and the various species of Melipona and Trigona being stingless

The sting and the 2 venom glands present the same structure as found in the wasps although the whole apparatus is somewhat more improved and shows wide variations throughout the apids

Like all animal venins bee venom is proteinous in character It is digested by pepsin papain and trypsin Although many physicochemical researches have been made with it no serious attempt has been made to ascertain its real chemical composition All we know is that it presents one or more

neurotoxins and is proteolytic and hemolytic in large doses Of the neuro toxins one manifests a particular tropism for the central nervous system another for the autonomic system the former causing depression somnolence and coma while the latter produces diarrhea abdominal pain cramps nausea and vomiting arterial hypotension and tachycardia Proteolysin is responsible for the local swelling and the spreading edema together with hemolysin it causes blood destruction and hemorrhages in the lungs intestines and other viscera In large doses especially in cases of multiple stings at the same time the patient is apt to develop some symptoms which resemble tetanus trismus contracture and restlessness

For prevention of the disagreeable symptoms following bee stings an excellent procedure consists in the active immunization of those who are engaged in the manufacture of honey This may be achieved by repeated injections of gradually increasing doses of anavenin that is bee venom that has been detoxified by formalin and heat

Since no specific treatment is available therapeutic measures are the same as those used to combat the effects of wasp poisoning

It must be borne in mind that for the last decade bee venom has been used to combat pain in the treatment of neuralgia neuritis and arthritis For this purpose it must be carefully secured diluted and preserved against deterioration and contamination When injected subcutaneously or intradermally this solution gives some relief to persons with those symptoms

FISH AND LAMPREYS

Quite a few species of fish and lampreys are known to venenate human beings Venenation may be accomplished as a result of handling stepping on or eating certain forms

According to M Phisalix (1922) venomous fish and lampreys may be divided into 3 categories (1) veneniferous forms (2) poisonous meat forms and (3) poisonous blood forms

Veneniferous Forms

From a toxicologic standpoint veneniferous forms may be divided into 3 subgroups (A) those bearing hollow dorsal spines connected with one basal serous gland (B) those bearing needle like double grooved spikes each spike provided with 2 lateral serous glands and (C) those bearing saber like, dentate spikes each spike provided with 2 marginal serous glands

A The most conspicuous forms among those bearing hollow spines with one basal gland belong to the family Batrachoididae (toadfish) subclass Teleostomi Acanthopterygii particularly the following

Batrachus tau and *B grunniens* both common in the Caribbean Sea and frequently encountered along the East coast of Central America

Thalassophryne maculosa abundant in the western Atlantic especially along the east central coast of Brazil

In this group the venom apparatus consists of (a) sharp, hollow spines protruding backwards from the free border of the opercle, and 2 or 3 (2 in Thalassophryne 3 in Batrachus) implanted in a ray like manner, just in front of the dorsal fin, each dorsal spine being covered by a fold of skin which evaginates at the proper moment, and (b) an acinous, serous gland located at the base of each spine, so that at the lightest squeezing or pressing of the gland the secretion immediately flows into the spine canal and emerges through the opening found very close to the tip

B The most important forms among those bearing needle like, double grooved spikes with 2 lateral glands belong to the following groups

(1) Selachii (shark like fish), family Dasyatidae (sting rays)

Dasyatis centroura, found in the Atlantic and the Mediterranean *D margarita,* common in the tropical Atlantic along the west coast of Africa *D pastinaca,* also found in the Atlantic and the Mediterranean

Taeniura grabata, in the east Atlantic, Mediterranean, and Red Sea, *Urolophus torpedinus,* in the Caribbean, along the coast of Central America

(2) Teleostomi Acanthopterygii (bass, mackerel, and perch) family Trachinidae (weevers), with 2 sets of poison barbs on the operculum and on the dorsal fin

Trachinus draco and *T vipera,* in the Atlantic and Mediterranean, from Europe to northern or western Africa

Family Triglidae (gurnard), often with numerous rays

Cottus bubalis, in the north Atlantic and Baltic Sea, *C gobio* and *C tricuspis* in the north Atlantic and Artic Ocean

Scorpoena brasiliensis, along the coast of Brazil

S grandicornis, in the tropical Atlantic and the Caribbean Sea (Cuba especially), *S plumieri,* also in the tropical Atlantic from Florida to Colombia, *S porcus,* in the Atlantic and Mediterranean, *S scrofa,* also in the Atlantic and Mediterranean

Synanceia verrucosa, in the Red Sea and the Indian Ocean especially in Polynesia where it digs into the sand near the coast It is known as "noho" in Tahiti and laffe" in the Reunion Islands

C The outstanding forms among those bearing saber like, dentate spikes with 2 marginal glands, belong to the family Siluridae (catfishes), Physostomi (carp catfish, and eels), particularly the following

Arius hertzbergii, found both in rivers and in the tropical Atlantic (Brazil and Guianas)

Doras muricus, in the southwest Atlantic (from Brazil to Argentina)

Pimelodus maculatus, in the tropical Atlantic and the Caribbean (from northeastern Brazil to the West Indies)

Piramutana blochii common in rivers in Brazil

Plotosus anguillaris very abundant in the Indian Ocean from east Africa to Polynesia where it is called "ikan sambilan," and Japan, where it receives the name "giggu," while in Mauritius it is designated "machoira "

Silurus japonicus, found in rivers of both China and Japan

The venom is a bluish clear liquid, becoming milky or opalescent after the death of the fish It is neutral in reaction, is soluble and preservable in glycerine and when heated in glycerine at 100° C for 1 hour loses its neurotoxicity but keeps its phlogogenous properties

The effect of the venom is rapid particularly on small animals Composed of neurolysin, proteolysin, and hemolysin, its introduction into the body causes local pain bloody swelling and necrosis with lymphadenitis, followed by numbness of the limb, headache, shivering, dyspnea, vomiting, fainting, tonic and clonic convulsions, and paralysis, eventually death

Therapeutic measures are merely symptomatic Potassium permanganate, adrenalin and local anesthetics are helpful

Poisonous Meat Forms

Forms possessing poisonous meat may be found among the 2 main groups lampreys and fish

Lampreys—Some species in the family Petromyzontidae (Cyclostomata) and particularly *Petromyzon fluviatilis* common in the rivers of the Amazon basin, are known to cause severe poisoning when eaten

Fish—Many species of the most heterogeneous groups are known to be poisonous

A Selachii (shark like fish) family Carcharidae (sand sharks)

Carcharias glaucus, common in European waters, where it is called "requin bleu"

B Teleostomi Acanthopterygii (bass, mackerel, and perch) family Carangidae (pompanos)

Caranx crumenophthalmus, common in tropical waters in the Atlantic, Caribbean Mediterranean Red Sea and Indian Ocean Names "chicarro in Cuba and "coulirou" in Guadeloupe

Family Labridae (wrasse fish)

Pseudoscarus chrysopoma and *P superbus*, the former in the Pacific and Indian Oceans (East Indies), the latter in the Caribbean Name "vieja" in Cuba

Order Pediculati (anglers and batfish)

Malthe vespertilio wide spread in tropical Atlantic and Caribbean (from northeastern Brazil where it is called "guacucuja or morcego to the Guianas Venezuela, Colombia, and the West Indies)

Family Percidae (perch bass and groupers)

Mesorprion griseus, in the tropical Atlantic, from west Africa to Cuba Central and South America Names "serrano" or, in Cuba "caji"

Family Sparidae (porgies)

Lethrinus nematacanthus, in the northwest Pacific and the Japanese Sea Name "mambo" in New Caledonia

Family Sphyraenidae (barracuda)

Sphyraena picuda (S barracuda) and *S vulgaris* are common in the Caribbean

C Physostomi (carp catfish, and eels), family Clupeidae (herring)

Clupea humeralis and *C thrissa*, both common in warm waters of the Atlantic and Caribbean, *C perforata*, in the Indian Ocean (Malay) and *C venenosa* in the tropical Pacific and the Indian Ocean (*C thrissa* is the machuelo' of the West Indies)

Engraulis boelema, common in sandy places in the Red Sea and the Indian Ocean Name ' bara

Family Muraenidae (moray s)

Anguilla vulgaris (*A vulgaris* in Europe, *A chrysypa* in North America), found both in fresh water and in the Atlantic

Conger conger, found in Europe and the West Indies Name "conger eel '

Family Belonidae (houndfish)

Tylosurus caribboeus, common in the Caribbean

Family Hemiramphidae (halfbeaks) abundant in the Atlantic Name in Brazil "agulha "

D Teleostomi Plectognathi (globefish), family Balistidae (triggerfish)

Alutera monoceros, Balistes carolinensis, both common in the tropical Atlantic and Caribbean

Family Ostraciidae (trunkfish)

Ostracion trigonus, in the Caribbean

Family Tetrodontidae (puffers)

Chilomycterus orbicularis and *C tigrinus*, in the Indian and Pacific oceans *C reticulatus*, in the tropical Atlantic

Diodon hystrix, widespread from the south Atlantic to the Indian and the Pacific oceans

Tetrodon heraldi, in the tropical Atlantic (West Indies and Brazil where it is called ' baiacu '), *Lagocephalus laevigatus, Tetrodon ocellatus*, and *T reticulatus*, in the China and Japanese seas (Japanese name "kanabuku"), *T sceleratus*, in the Indian and the Pacific oceans down to Australia, *T stellatus*, in the Indian Ocean (East Indies), *T hispidus*, the "death fish" of Hawaii

Poisoning—The meat of all of these species, and of some others as well, is known to cause serious accidents* When the fish is young it seems to be atoxic but when it is mature and particularly during the mating period, it becomes more and more poisonous so that in some countries strict legislation forbids the sale of quite a few of these adult forms Gonads, eggs, and liver are responsible for most accidents

The toxicity of the tissues may be due to the exaggeration of the metabolic changes of such fish, thus enhancing the retention of poisonous principles in their organs especially following their sexual activity

The poisoning, called "cigatuera" in the West Indies and "fugu in Japan, has been attributed to a toxalbumin (in the old classification) or to a substance vaguely called tetrodontin, which on human beings and animals causes the following symptoms soon after the fish has been eaten nausea

*E g Kingfish (*Scomberomorus caralla*) and a species of sprat sardines *Clupeda longiceps* found off Ceylon

vomiting diarrhea headache restlessness cyanosis hypothermia paresis paralysis and sometimes death In a few cases poisoning may be caused simply by contact of the skin of a human being with the tissues of the fish the following symptoms having been noticed itching urticaria chills and salivation

Therapeutic measures are evacuation of the intestinal tract and stimulants

Poisonous Blood Forms

Forms with poisonous blood may also be found among the 2 principal groups lampreys and fish

Lampreys—One species of the genus Petromyzon (*P marinus* family Petromyzonidae class Cyclostomata) is particularly considered hematoxic it lives in the north Atlantic and the Mediterranean

Fish—A few species are recognized as poisonous

A Selachii (shark like fish) family Rajidae (skates)

Raja clavata common in the east Atlantic between Europe and Africa

Torpedo marmorata found in the east Atlantic and the Mediterranean

B Physostomi (carp catfish and eels) family Muraenidae (morays)

Anguilla vulgaris (*A vulgaris* and *A chrisypa*) found both in fresh water and in the Atlantic (Europe and North America)

Conger conger the conger eel of Europe and the West Indies

Muraena helena in the Mediterranean waters

Poisoning—This group seems to occupy a position intermediate between the preceding ones As a matter of fact it is of more scientific than clinical interest because since only the blood is poisonous it is sufficient to boil the fish to eliminate the danger

Ichthyotoxin is the name that has been given to the principle in fish blood responsible for the toxic effects It is bound to blood serum and is inactivated on boiling When injected into laboratory animals it causes lysis of both red cells and leucocytes retardation of blood clotting convulsions and paralysis with hypothermia and difficulty in respiration and circulation

When ichthyotoxin is injected with fish serum into an animal both active and passive immunity may develop so that production of an antiichthyotoxin is feasible It is neutralized or inactivated by bile and antiserum for *Naja naja* venom

The physicochemical mechanism of ichthyotoxin action seems to lie in a colloidal precipitation as revealed by mixing fish serum or blood or tissue extract with the serum of any other animal

LIZARDS

Only two species of lizards are known to cause poisoning Both belong to the family Helodermatidae (class Reptilia order Squamata suborder Sauria) genus Heloderma

The species *H suspectum*, the Gila monster is found in the United States (New Mexico Arizona extreme southern Utah and Nevada) while *H horridum* lives in the west and south of Mexico and in the north of Central America

Venom Apparatus

In the Gila monsters, all the teeth are more or less definitely grooved On each side of the lower jaw is a gland which secretes saliva, which the lizard can inject into its enemy when biting Its secretion is a modified, toxic saliva that constantly exudes from the mouth of the lizard in the course of feeding, being ejected through contraction of the muscles which intervene in mastication, particularly of an expansion of the mandibular coronoidal muscle

The venom is typically neurotoxic, affecting the central nervous system Soon following the bite, the venom acts on the respiratory center, causing microscopic changes in the ganglia cells It is devoid of any proteolytic or tissue digesting activity and shows no direct hemolytic powers

Bites on human beings are known to cause pain and some swelling with discoloration, followed at times by cold perspiration, faintness, and drop in blood pressure, death takes place only in very exceptional instances

Treatment is merely symptomatic

POISONOUS SHELLFISH

Six species of the genus Conus are known to cause poisoning by bites *C aulicus, C geographus, C marmoreus, C striatus, C textilis,* and *C tulipa* in the South Pacific The symptoms are pain, edema, ascending paralysis, coma, and death The treatment is symptomatic

POISONOUS CORALS, SEA ANEMONES, SEA URCHINS, AND JELLYFISH

All of these cause urticaria and other allergic phenomena, especially in sensitive persons Wounds caused by the spines of sea urchins, *Tripneustes esculentus* and *Centrechinus antillarum,* as well as the Portuguese man of war (Physalia), may suppurate The treatment is symptomatic

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CHAPTER 59

DISEASES DUE TO NUTRITIONAL DISTURBANCES

ANTONIO CLERCH RIUS

GENERAL CONSIDERATIONS

The study of diseases produced by nutritional deficiencies is of extraordinary importance in the field of medicine. Many organic disturbances both in children and in adults are caused by dietary deficiencies with their concomitant sequelae so that an individual who might, with correct diet, be free from general disturbances is subject to many disorders in this field of pathology. The problem is far reaching and quite complicated. In fulfilling the purpose of this chapter we shall sketch only very briefly the causal agents, pathogenesis, clinical symptoms, laboratory diagnosis and treatment.

Deficiency diseases are rather frequently caused by lack of

(1) Vitamin Deficiency
- Vitamin A
- Vitamin B complex, including B_1 or thiamine, the antineuritic and antiberiberi vitamin, B_2, or riboflavine, niacine, the antipellagric factor, B_6 or pyridoxine, para amino benzoic acid, pantothenic acid, biotin or vitamin H, B_{12}, choline, inositol, and B_c or folic acid
- Vitamin C (antiscorbutic)
- Vitamin P or citrin (antihemorrhagic)
- Vitamin D (antirachitic)
- Vitamin E (antisterility)
- Vitamin K (antihemorrhagic)

(2) Essential Amino Acids
- Lysine
- Tryptophane
- Phenylalanine
- Histidine
- Leucine
- Isoleucine
- Threonine
- Methionine
- Valine
- Arginine

(3) Essential Fatty Acids
- Linoleic acid
- Linolenic acid
- Arachidonic acid

(4) Nutritional Anemia
- Anemia due to iron deficiency
- Anemia due to deficiency of the antianemic principle (sprue, pellagra, macrocytic anemia of pregnancy, pernicious anemia or Addison Biermer disease, etc.)
- Anemia due to deficiency of vitamin C
- Anemia due to myxedema

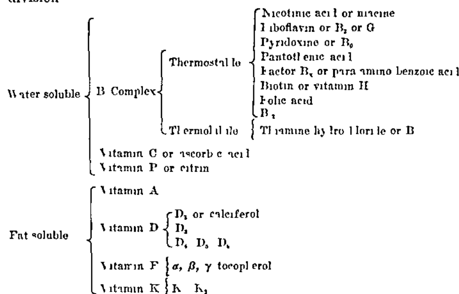
(5) Nutritional Edema

(6) Simple Goiter

(7) Mineral Deficiency
- Calcium
- Phosphorus
- Iron
- Iodine
- Etc

VITAMIN DEFICIENCY

For a better study of essential vitamins we have proposed the following division



VITAMIN A OR AXEROPHTHOL

(Antixerophthalmic, Antiinfectious, Growth Promoting)

Vitamin A is derived from carotene its provitamin The transformation of carotenes into vitamin A apparently takes place in the liver where an enzyme carotenase is present

SYMPTOMS OF VITAMIN A DEFICIENCY

Symptoms of vitamin A deficiency are manifested as (1) disturbance of vision (nyctalopia night blindness) (2) lack of growth (3) keratinization of the epithelia (4) lowered resistance to bacterial infection (5) defective development of teeth (6) nervous lesions, (7) genital disturbances

Visual Disturbances

Since the time of the ancient Egyptians the disease known as night blindness (nyctalopia) has been treated by a diet based on liver Hippocrates in ancient Greece treated it in the same manner It has been observed among mariners making long voyages and among prisoners and slaves It was observed among soldiers of World War I Cases have occurred in Russia Japan, India, and other countries In the United States Jeghers was able to prove decreased capacity for adaptation to darkness on the part of some children, in experiments carried out before 1937 There is a substance in the retina, called *visual purple* or *rhodopsin*, contained in the retinal rods which bleaches when exposed to intense light The ability to regenerate depends upon whether the diet is rich in vitamin A or not When the diet is rich in this vitamin regen

eration is rapid, when it is poor in vitamin A recovery is slow This capacity for regeneration is linked with a capacity for adaptation to darkness and is directly related to the speed with which the visual purple is regenerated, slow adaptation or lack of adaptation is called *nyctalopia* or night blindness

Lack of Growth

Vitamin A deficiency is manifested by slow body growth which is observed not immediately but only after a certain lapse of time It has been demonstrated experimentally that this vitamin is stored in the liver and to a less degree in the kidneys and lungs so that variation in diet one time rich again poor in this vitamin is not immediately evident in the animal

Keratinization of the Epithelia

Keratinization of the epithelia is manifested in the mucosa of the respiratory passages urinary pathways salivary glands conjunctiva cornea etc

Keratinization of the epithelia of the cornea and of the conjunctiva leads to desiccation of the ocular conjunctiva accompanied in addition by a series of symptoms such as photophobia Bitot s spots light brown pigmentation of the conjunctiva and later softening and degeneration of the cornea These disturbances may lead to complete and permanent blindness (xerophthalmia and keratomalacia)

Lowered Resistance to Bacterial Infection

As a result of the epithelial disturbances produced by deficiency of vitamin A the resistance of the epithelium to bacterial invasion is lowered and infection takes places generally by way of the bronchopulmonary lacrimal and salivary epithelia The type of infection varies according to the site of entrance Although the action of vitamin A on catarrhal states is still under discussion this vitamin is used at the present time as a preventive in these conditions

Defective Development of Teeth

In avitaminosis A teeth develop poorly due to defective development of enamel and dentine because of metaplasia of the ameloblasts and atrophy of the odontoblasts and ameloblasts

Nervous Lesions

Some authors have reported that vitamin A deficiency produces disturbances of the central nervous system and degeneration of the auditory nerve leading to deafness Moore demonstrated a type of nutritional blindness due to vitamin A deficiency which is caused by death of the optic nerve

Genital Disturbances

It has been observed that lack of vitamin A produces atrophy of the testicle in the male rat and keratinization of the vaginal epithelium in the female The deficiency later results in necrosis and infection of the decidua materna the fetus dies as a result of the nutritional disturbance

FOODS CONTAINING THE HIGHEST PERCENTAGE OF VITAMIN A

The following foods contain the highest percentage of vitamin A

Spinach	Cod liver oil	Lentils	Cauliflower	Brain
Tomatoes	Liver	Avocado	Lettuce	Oysters
Green cabbage	Whole wheat bread	Oranges	Carrots	
Lemons	Kidneys	Raw milk	Mushrooms	
Bananas	Plums	Egg yolk	Butter	
Cocoa	Yeast	Herring	Turnips	

VITAMIN A REQUIREMENTS

It has been calculated that about 20 to 30 I U per kilogram of weight in adults weighing approximately 70 kg is indispensable to prevent night blindness For children from 2 to 14 years of age 6 000 to 8 000 I U daily are necessary

The requirements for a woman are 5 000 I U according to other authors the requirements are 10 000 I U Vitamin A concentration in the body will be found to be diminished or lacking when not present in food or when ingested in too small quantities However even though vitamin A or carotene or provitamin may be ingested there still may be a vitamin A deficiency if the subject has certain alterations such as (1) disturbance in absorption of fats which occurs in serious affections of the pancreas and in obstructive jaundice etc (2) *affections of the parenchyma of the liver (3) hepatic icterus atrophic and hy*pertrophic cirrhosis (4) Basedow s disease in which there is an increased consumption of vitamin A (5) myxedema in which insufficient transformation of the provitamin into vitamin A takes place and (6) certain cachectic states such as advanced neoplasms and pulmonary tuberculosis In these cases the vitamin is eliminated in the urine because of excessive permeability of the kidney This is not true in other cases nor when doses of the vitamin are administered in normal cases

LABORATORY DIAGNOSIS

Diagnosis of hypovitaminosis or avitaminosis A is made by examination of the blood and urine (See Gradwohl 1948)

TREATMENT

Treatment of hypovitaminosis A consists in administering vitamin A capsules in addition to a diet rich in vitamin A (codliver oil tomatoes plums etc)

In cases of avitaminosis A in addition to the diet rich in vitamin A 50 000 to 200 000 I U are administered daily If necessary higher doses may be given since few cases of hypervitaminosis A have been described to date Rosenberg and Veeberg state that it is possible to administer up to 100 000 units of vitamin A daily to mice without any resulting disturbance If the vitamin is not well tolerated when given by oral route it may be given parenterally in daily doses up to 36 000 I U

B COMPLEX

The importance of the vitamin B complex the antiberiberi or B vitamin is well known

VITAMIN B_1, THIAMINE

(Antiberiberi or Antineuritic)

Vitamin B_1 chemically is the hydrochloride of thiamine chloride

SYMPTOMS OF VITAMIN B DEFICIENCY

The symptoms of vitamin B_1 deficiency are (1) nervous disturbances (2) digestive disturbances (3) cardiac disturbances and (4) metabolic disturbances (See Chapter 61)

VITAMIN B_2, RIBOFLAVIN, VITAMIN G, OR LACTOFLAVIN

Vitamin B_2 was formerly called in North America vitamin G It is now better known as *riboflavin* a name derived from its chemical composition

SYMPTOMS OF VITAMIN B_2 DEFICIENCY

In experimental animals deficiency of vitamin B_2 is manifested by decrease and then cessation of growth in rats this is accompanied by blepharitis conjunctivitis eczema of the skin around the eyes and cataract in chicks by muscular paralysis in dogs by slowing of the respiration (bradypnea) and lowered temperature All of these symptoms disappear after administration of riboflavin

In 1938 Sebrell and Butler produced experimental B_2 avitaminosis in a group of volunteers who developed cracked lips with maceration and fissure of the labial commissure and seborrheic accumulations in the nasolabial folds These symptoms characterize vitamin B_2 deficiency The condition is called *ariboflavinosis*

In serious cases in addition to these symptoms nervous changes develop manifested by torpid movements accompanied by myeline degeneration of the peripheral nerves and of the posterior horn of the medulla as demonstrated experimentally by Street Cowgill and Zimmerman also vascular extravasation around the iris followed by superficial vascularization of the cornea and interstitial keratitis At times there are in addition photophobia nebulous vision congestion of the scleral coat and opacity of the cornea

FOODS CONTAINING VITAMIN B

The following foods contain vitamin B_2

Bananas	Dry yeast	Beef	Apples
Spinach	Turnips	Liver	Oranges
Eggs	Potatoes	Milk	Cheese

VITAMIN B_2 REQUIREMENTS

Opinion regarding vitamin B_2 requirements is divided Rose reported the requirements as 400 units for children up to 10 years of age or in deficiency

cases 20 units per each 100 calories if more than 2 000 calories are consumed For adults 20 units per each 100 calories are recommended Stiebeling recommends 450 to 600 units per day Recently 2 mg are considered the daily requirements of adults

TREATMENT

In cases with vitamin B_2 deficiency 500 units should be given orally per day in slight cases 600 to 800 I U daily orally in serious cases In addition the patient should be kept on a diet rich in vitamin B In the U S A 2 to 15 mg or more are given daily

VITAMIN B_X OR B_X FACTOR (ANTIGRAY HAIR) OR P AMINO BENZOIC ACID

Morgan Ausbacher and Martin showed that when p amino benzoic acid was added to the diet the graying hairs of the experimental animals regained their normal color In recent work Sieve administered 200 mg daily of p amino benzoic acid to 50 gray haired experimental animals with the result that the normal pigmentation was restored after 2 months

The importance of this work has not yet been determined in human beings

VITAMIN B_6, ADERMIN, PYRIDOXINE OR THE I FACTOR

Vitamin B_6 was described by Lepkovsky Jukes and Kruse as the I factor It was shown that the dermatitis in rats may be due to lack of a new substance which formed a part of the B complex and which has been given the name B_6 Since Gyorgy called the condition produced in rats *acrodynia* the new substance was designated as *antiacrodynic factor,* other authors called it *adermin* Despite this work it was not until 1938 that Kuhn and Harris and Folkes obtained the chemical formula of this product as well as its synthesis

SYMPTOMS OF DEFICIENCY

The work of Spies Bean and Ashe, with patients presenting symptoms of extreme nervousness irritability insomnia debility muscular rigidity difficulty in walking and stomach cramps showed that the intravenous administration of 50 mg of vitamin B_6 brought these subjects back to normal

Some authors state that they have obtained satisfactory results in Parkinson s disease although to date the specific action in this condition cannot be stated

FOODS CONTAINING VITAMIN B_6

Foods containing vitamin B_6 are

Meat (muscle of mammals)	Yeast	Rice
Fish	Wheat	Liver
	Corn	

VITAMIN B_6 REQUIREMENTS

The daily quantity of vitamin B_6 necessary to prevent hypovitaminosis or avitaminosis B_6 can be obtained in the average amount of such foods as rice

wheat bread corn and fish Hypervitaminosis B₆ apparently Kark has administered up to 1 160 mg daily orally to pati toxic effects

TREATMENT

A dose of 1 to 3 mg of this vitamin should be given daily

ANTIPELLAGRA VITAMIN (PP)

Nicotinic Acid Nicotinamide Niacin

Deficiency of this vitamin results in the condition kn Pellagra is discussed in Chapter 62

PANTOTHENIC ACID

This factor of the B complex called factor 2 by Lepkov after adsorption of vitamins B_1 B_2 and B_6 by infusori synthesized in 1940 by Williams and Major It has been demon crystal form was obtained that it contains β alanine

SYMPTOMS OF DEFICIENCY

In the chick deficiency of this vitamin causes a derm eyes mouth and feet in the mouse a change in the c (graying) in the rat retardation of growth accompanie necrosis

It is required in man during the early years as a condit velopment and it has been considered important as a factor of the hair although this role has not as yet been specifically

FOODS CONTAINING PANTOTHENIC ACID

Yeast	Eggs	Liver
Whole rice	Heart	Kidneys

PANTOTHENIC ACID REQUIREMENTS

Daily pantothenic acid requirements are not known Williams about 11 mg daily are needed to prevent sympton

Since this factor is found widely in all animal and plant microorganisms as well as higher animals also require it for importance to the human being may well be understood

TREATMENT

Diet rich in this factor is needed with the addition of by the oral route Since the substance is not toxic it may

VITAMIN H OR BIOTIN

Wildiers (1901) recognized that yeasts required an additional element for growth which he called "bios." Lucas separated this factor into 2 component parts, calling them bios I and II. In 1928 Eastcott called bios I "i-inositol." Later work by Gyorgy (1931) resulted in finding a factor which he called vitamin H, which acted when an element contained in egg white produced harmful effects in man. In 1935 Kogl isolated *biotin*, one of the components of bios II, in its pure form; in 1940 Gyorgy and collaborators identified biotin as vitamin H.

SYMPTOMS OF DEFICIENCY

In rats there are present alterations of the skin, later accompanied by progressive emaciation leading to death.

In man changes in the color of the skin are produced, with resultant ashy color, with fissures and increased epithelial desquamation. There is accompanying lassitude, somnolence, muscular pains, precordial and anorexial discomfort.

In children a special reddish pigmentation is observed in the shoulder.

FOODS CONTAINING BIOTIN OR VITAMIN H

Pig liver	Yeast	Asparagus	Cereals
Beef liver	Eggs	Water cress	Nuts
Kidney	Milk	Lettuce	Fruits

VITAMIN H REQUIREMENTS

To prevent symptoms of vitamin H deficiency, 150 to 200 rat units per day should be given with the food. The rat unit is the daily dose needed to cure in 4 weeks the damage produced by egg white.

Egg white contains a substance which inhibits the action of biotin, called *avidin*. One gram of methylic ester of biotin corresponds to 27 000 000 rat units.

TREATMENT

For patients with symptoms of biotin deficiency, 150 to 300 γ of biotin should be administered parenterally per day.

FOLIC ACID

Snell and Peterson (1940), in work relative to "factors in bacterial growth," showed that certain acidilactic bacteria required extracts of plants or animals for their growth. Mitchell, Snell, and Williams (1941) found that *Streptococcus lactis* R grew better when placed in a medium containing a substance found in spinach. They called this substance "folic," in reference to its origin from leaves. The substance is now called the *L. casei* factor of liver, or glutamic acid.

SYMPTOMS OF FOLIC ACID DEFICIENCY

Reports in 1945 indicated that numerous cases of anemia of pregnancy were cured by the use of folic acid.

Symptoms of deficiency of folic acid are clear and determinative: hyperchromic macrocytic anemia accompanied by the clinical symptoms characteristic of this type of anemia. (See Chapter 60.)

FOODS CONTAINING FOLIC ACID

Beef and pork liver
Yeast

FOLIC ACID REQUIREMENTS

It is not possible at the present time to evaluate the daily requirements of f[illegible] although the fundamental importance of folic acid in preventing [illegible] ork of Spies on the use of folic acid in [illegible] pellagra and sprue in human [illegible] s (1945) carried out experiments on the treatment of [illegible] lic acid the synthesis of which in 1945 facilitated its use

TREATMENT

Spies recommended administration of 10 to 400 mg daily orally or parenterally but an average dose of 20 mg daily may be used in a large number of cases

VITAMIN B_{12}

This is an essential growth factor It is used in the treatment of sprue and pernicious anemia

VITAMIN C (ANTISCORBUTIC)

Ascorbic Acid

Scurvy is a condition which has been known from remote times long before it was recognized as a deficiency disease Hippocrates appears to have described it and Pliny related that a disease like scurvy attacked the army of Germanicus on the Rhine

Joinville in the 13th century at the time of the eighth crusade described the army of St Louis in Egypt as suffering from scurvy Later the disease was observed on long voyages undertaken in the era of great conquests and among prisoners in fact wherever fresh food was not available In the Franco Prussian War of 1870 1871 during the siege of Paris this disease was observed among the civilian population among the wounded in hospitals and among the prisoners The disease was described during the siege of Port Arthur in the Russo Japanese War and also during World War I

Holst and Frolich (1912) produced scurvy experimentally in the guinea pig In 1928 Szent Györgyi isolated ascorbic acid from the suprarenal cortex Later in 1932 Waugh and King obtained it from lemon juice (juice from the rind of the lemon)

The pure product was obtained from the suprarenal by Haworth Karrer and Von Euler and this permitted study of its chemical structure It was synthesized in 1933 by Reichstein The chemical structure is that of a hexuronic acid and chemically it corresponds to a lactone of [illegible] acid

It was named ascorbic acid by Haworth and Szent Györgyi and is also known as cevitamic acid

SYMPTOMS OF DEFICIENCY

Scurvy is characterized by diminution in capillary resistance with appearance of hemorrhages in compressed parts of the skin and in the gums The gums puff up and become spongy the teeth become loose due to rarefaction of alveolar bone and may fall out secondary infection may set in

The vitamin is thought to play an important part in the formation of intracellular colloidal substances of mesenchymatous origin such as the collagen of the fibrous tissues materials of nonepithelial character which hold tissue together including substances in the capillary walls dentine and cartilage

Osteoporosis develops in the young and may lead to fracture of bone The periosteum separates from the bone accompanied by pain in the joints and bones and swelling of the joints

The dental disturbances are due to poor formation of dentine, as a result of degeneration of the odontoblasts

Atrophy of the bone marrow is observed with deficient formation of blood cells and platelets In chronic scorbute there is a suprarenal hypertrophy at the beginning followed by atrophy Digestive disturbances such as gastric intolerance and diarrhea are present in these cases

In the child deficiency of vitamin C produces the so called infantile scurvy or Moller Barlow disease characterized by anemia and puffing up of the epiphyses of the bone accompanied by great pain due to subperiosteal hemorrhage When teeth are developed gingivitis is present with gingival hemorrhage and swelling of the gums around the teeth

FOODS WHICH CONTAIN VITAMIN C

Berries	Lettuce	Strawberries	Liver	Celery
Grapes	Turnips	Cherries	Kidney	Potatoes
Bananas	Rutabaga	Asparagus	Whole milk	Water cress
Oranges	Red beets	Spinach	Onions	Cauliflower
Lemons	Pears	Beef	Plums	Tomatoes
Apples				Cucumbers

VITAMIN C REQUIREMENTS

Vitamin C requirements vary with age sex and the general state of the individual

In newborn infants vitamin C requirements are 10 to 30 mg daily, in older children 20 to 60 mg , adults 25 to 75 mg , during lactation 100 to 150 mg daily

Prophylactically in newborn infants 10 mg daily in older children 20 mg and in adults 25 mg are needed to prevent scurvy In cases of increased metabolic activity as in pregnancy lactation fever hyperthyroidism etc the vitamin C requirements are greater and a larger quantity must be taken Not only an insufficient intake of the vitamin, but also deficient absorption or excessive elimination as in vomiting and diarrhea may result in vitamin C deficiency

TREATMENT

In the treatment of scurvy 100 to 150 mg of vitamin C are given daily In infantile scurvy 25 to 50 mg are administered orally With the pure ascorbic acid the patient must be put on diets containing tomato juice lemon orange etc foods rich in vitamin C

In serious cases of scurvy, larger doses of the vitamin may be given orally or parenterally provided no toxic symptoms appear From 100 to 200 mg may be given daily parenterally

VITAMIN P OR CITRIN

Vitamin P is found united with ascorbic acid in the juice of citrus fruits Szent Gyorgy showed that deficiency of vitamin P contributes to production of capillary hemorrhage since it governs capillary permeability Chemically it is a mixture of the glucosides hesperidin and eriodictin

VITAMIN D (ANTIRACHITIC)

Vitamin D is of extraordinary importance in the diet Lack of vitamin D especially in children produces a serious condition called *rickets*

Rickets has been known in England for centuries It was first described by Whistler in 1645 and by Glisson in 1650 Later authors attributed it to various causes The work of Mellanby and McCollum brought to light the knowledge that rickets is produced by deficiency of the D factor

The provitamin which is found principally in higher animals and in man is the 7 dehydrocholesterol which upon irradiation forms vitamin D_3 In lower forms principally in yeasts and plants ergosterol is found which when irradiated forms vitamin D_2 called *calciferol* by the British and *viosterol* by the Americans

In the study of vitamin D it is necessary to keep in mind its close relationship with the calcium and phosphorus metabolism of the organism

SYMPTOMS OF DEFICIENCY

Symptoms of vitamin D deficiency may be divided into 4 groups bone changes dental changes metabolic changes general changes

Bone Changes

Bone changes are characterized by alteration in ossification which lead to rickets in children and osteomalacia in adults

Rickets is characterized generally by changes in the line of *epiphyseal* ossification evidenced by a wide irregular girdle about the epiphysis which may be noted on palpation There is retardation in the process of ossification of the cranium with abnormal softness the disorder being known as *craniotabes* changes in the shape of the cranium such as the Olympian brow and arch of the palate occur the so called *rachitic rosary* characterized by the thickening of the chondrocostal zone of the ribs so that it feels like beads on a rosary thus accounting for the name deformity of the thorax and lower limbs known in clinical terms as genu valgum genu varum and genu recurvatum Osteomalacia is generally a disease of adults characterized by abnormal softness of all bones but principally of the femur and pelvis There is difficulty in walking accompanied by relaxation of the skeletal muscles alternating with hypertonicity of some muscle groups such as the adductors of the thigh

Dental Changes

Dentition is delayed and there are difficulties in implantation and defects in form There are changes in calcification in enamel and dentine resulting in diminished thickness of the dentine which then is not homogeneous and not compact but has intercellular spaces Enamel presents an irregular and eroded surface sometimes pigmented

Metabolic Changes

Changes in calcium and phosphorus metabolism are present The inorganic phosphorus content of the plasma is lowered by increase in excretion of phosphorus which is eliminated in greater proportion than normal Increased excretion of phosphorus results in its decrease in the blood with movement of phosphorus from bone tissue to maintain the blood level This results in changes in the bones since the calcium phosphorus ratio cannot be maintained Blood calcium is generally within normal limits when it is low tetany results but this is rare in rachitic individuals There is excessive elimination of calcium through the intestines while no fixation of calcium in the bone is taking place

General Changes

General changes are hypotony muscular debility hepatomegaly splenomegaly abdomen increased in bulk profuse sweating and anemia

FOODS CONTAINING VITAMIN D

Codliver oil	Sardines	Mother s milk
Cow s milk	Salmon	Oysters
Codfish	Cream	Wheat
Egg yolk	Butter	Barley
		Oats

VITAMIN REQUIREMENTS

It has been estimated that the daily requirements for vitamin D are for the newborn 400 to 500 units during adolescence 500 to 600 units daily and in the average adult about 700 units although adult requirements have not as yet been satisfactorily determined In pregnancy and lactation a dose of 800 units has been suggested with a diet high in calcium and phosphorus

TREATMENT

In the treatment of rickets doses ranging from 1 000 units in the beginning of the disease to 60 000 units in serious cases should be used daily Some authors have employed massive doses of vitamins in the treatment of rickets Garraham and Ruiz used up to 600 000 units orally in a single dose without any resulting toxic symptoms In the adult up to 150 000 units may be used daily in refractory cases

Care should be taken to prevent hypervitaminosis D Hypervitaminosis D results in toxic changes manifested by headache nausea profuse sweating anorexia loss of weight profuse diarrhea and renal insufficiency

VITAMIN E OR TOCOPHEROL

Antisterility Vitamin

The existence of this vitamin has been suspected since 1920 following investigations by Mattill It was not until 1921 however that Evans Bishop Sure and others observed need for further information *In 1938 Evans and Emerson succeeded in isolating the pure* vitamin, later in the year it was synthesized by Karrer

Vitamin E is composed of 3 tocopherol substances *α* *β* and *γ* *β* and *γ* being less active than the *α* tocopherol

SYMPTOMS OF DEFICIENCY

In the female rat the fetus dies and is reabsorbed after 8 to 20 days of pregnancy due to alterations in the placenta

The male rat presents testicular atrophy with degeneration of the genital epithelial tissue of the seminiferous tubes

In human beings studies by Vogt Moller Watson and Tew and others have demonstrated that women who have had frequent abortions and abnormal parturition with death of the fetus experienced normal pregnancies and parturitions with normal offspring following treatment with vitamin E

FOODS CONTAINING VITAMIN E

Codliver oil	Egg yolk	Water cress	Bananas
Olive oil	Herring	Milk	Lettuce
Whole wheat	Butter	Oats	Cocoa
White flour	White bread	Barley	

VITAMIN E REQUIREMENTS

Vitamin E requirements have not as yet been determined for man or lower animals

TREATMENT

In treatment of vitamin E deficiency 20 mg daily in oil are given intramuscularly or per os or 50 mg according to Mero equivalent to about 40 I U

VITAMIN K (ANTIHEMORRHAGIC)

In 1929 Dam called a factor present in alfalfa *vitamin K* using the first letter of the Danish word Koagulation for this vitamin

In 1940 Doisy and co workers discovered the chemical structure of vitamin K_1 Vitamin K is formed by 2 distinct bodies vitamins K_1 and K_2 derived from the 2 methyl 1 4 naphthoquinone nucleus with different radicals having different solubilities

SYMPTOMS OF DEFICIENCY

Deficiency of vitamin K is manifested in adults and in children solely by the presence of hemorrhages due to decrease in prothrombin in the plasma in the newborn by intracranial hemorrhage

FOODS CONTAINING VITAMIN K

Hog liver	Carrots	Egg yolk	Cabbage	Spinach
Ox liver	Rice bran	Soybean oil	Alfalfa	Tomatoes

VITAMIN K REQUIREMENTS

Daily vitamin K requirements have not been determined It is believed that under normal conditions the minimum daily requirements are obtained aside from that taken in in food by synthesis of the vitamin in the lower intestinal tract by certain bacteria (Kolmer)

TREATMENT

According to Dam administration of 5 to 10 mg of 2 methyl 1 4 naphthoquinone or 10 mg of diacetate of 2 methyl 1 4 naphthoquinone is recommended for adults given orally These products have been used intravenously with good results

In serious cases Cheney advises administration intravenously of 1 to 3 mg of 2 methyl 1 4 naphthohydroquinone 3 sulfonate of sodium When using this product care must be taken to prevent disturbances produced by hydroquinone such as vomiting and porphyrinuria Doses of 10 30 and up to 50 mg daily do not produce disturbances Diet high in vitamin K should be associated with the treatment

ESSENTIAL AMINO ACIDS

Amino acids are components of protein very plastic substances deficiency of which in the diet results first in cellular autophagy and later in death of the organism Amino acids considered as indispensable are those not synthesized by the organism those that are synthesized would not be lacking since they are contained in the cells

The essential or indispensable amino acids therefore are " those amino acids the ingestion of which in food is indispensable and lack of which results in disorders which may cause death since these substances cannot be synthesized by the human organism "

Ten have been described as essential lysine tryptophane phenylalanine histidine leucine isoleucine threonine methionine valine and arginine

LYSINE

According to Osborne and Mendel this acid is vital for growth

TRYPTOPHANE

Deficiency of tryptophane in the diet which is indispensable for maintenance of body weight produces cataracts and other ocular changes (Trotter and Day)

When tryptophane is lacking in the diet of animals blindness occurs accompanied by white opacity and loss of color of the eye (Curtis Hauge and Kraybill 1932) When catabolic activity is retarded tryptophane accumulates especially in the thyroid gland the erythrocytes and in the pancreas when it is in a state of digestive repose it is believed that it forms a part of both the external and internal secretions of this organ

Tryptophane is closely linked with the formation of melanins substances originating within epithelial cells or their derivatives (melanoblasts)

PHENYLALANINE

Phenylalanine is thought to be an intervening factor in the formation of pigment The work of Womack and Rose in 1936 demonstrated that it is indispensable in nutritional processes and that omission of it from the diet produces phenylketonuria not infrequently observed in retarded children A strengthening action upon the exhausted heart is attributed to phenylalanine and in the process of increasing caloric production up to as much as 18 per cent

HISTIDINE

Histidine in union with tryptophane is considered hematogenous and anabolic as well as a possible precursor of the purines Since histidine is the precursor of histamine deficiency may lead to anemic states and to production of gastroduodenal ulcers

Studies by Kobsch in 1936 demonstrated that histidine favors blood circulation of the mucosae with increase in tone and disappearance of spasm in these structures

LEUCINE

Leucine intervenes in body growth and is ketogenic exerting action on the exhausted heart

Investigations have shown that it is a preponderant factor in the growth of both the Koch and the Hansen bacilli

ISOLEUCINE

Isoleucine forms an integral part of the histones which in turn are included in some simple proteins called globins It is thought to be a valuable factor in influencing growth and development of the body

THREONINE

Threonine was found in 1931 by Rose in casein while he was experimenting on the physical growth of rats He noticed that this substance exercised influence upon growth Womack and Rose (1935) demonstrated the presence in casein of two factors which influence body growth isoleucine and threonine

METHIONINE

Methionine is indispensable for the growth of the body It is important in metabolism because of the sulfur contained in its molecule A greater intake of this acid than normal is required in lactation

Deficiency of methionine causes alterations in fat metabolism with fatty accumulation in the liver This change is extended to cholesterol and to the cholesterol esters It has been called the lipotropic' factor Absence of methionine occasions cirrhosis of the liver and fatty degeneration of the kidney manifested by hemorrhagic necrosis of the renal cortex

Atrophy of the thymus, splenomegaly and hemolymphatic transformation of lymph glands, as well as hemorrhages in the eyes, have been observed as a result of deficiency of this amino acid.

VALINE

Deficiency of valine in the diet produces disturbances in growth as well as sensitivity to touch in animals and a distinct loss of coordination of movements.

Valine is found in casein from cow's milk and in chicken eggs. It is present in almost all human tissue, the thymus being the richest, harboring 8.1 per cent.

ARGININE

Arginine is considered essential in the production of purines and enters into the composition of phosphagen in invertebrates. By the action of a ferment called *arginase* it is decomposed into ornithine and urea.

Although arginine does not act directly with relation to body growth, it initiates cellular growth (Hammett and Elliott, 1935).

ESSENTIAL AMINO ACID REQUIREMENTS

The exact daily requirements of amino acids have not as yet been ascertained, but the percentage of the following in relation to the food intake *can be calculated individually: lysine, 1 per cent; leucine, 0.9 per cent;* phenylalanine, 0.7 per cent; valine, 0.7 per cent; threonine, 0.6 per cent; methionine, 0.6 per cent; histidine, 0.4 per cent; tryptophane, 0.2 per cent; and arginine, 0.2 per cent.

FOODS CONTAINING THE ESSENTIAL AMINO ACIDS

All protein substances contain essential amino acids in one form or another; they are found principally in:

Meat	Chicken eggs	Cow milk
Beef	Turkey eggs	Goat milk
Pork	Duck eggs	Donkey milk
Mutton		
Fowl		
Fish		

TREATMENT

In amino acid deficiency cases the amino acids must be administered orally in food or parenterally, either in the form of polypeptides or as isolated amino acids.

ESSENTIAL FATTY ACIDS

In 1929 Burr and Burr demonstrated the presence of unsaturated acids such as the linoleic and linolenic acids which are essential in the diet for normal growth of rats.

In 1938 Turpeinen found arachidonic acid essential for the maintenance of life in mice. Later Nunn and Smedley MacLean established the fact that arachidonic acid is deposited in the liver.

These fatty acids are found in nature in plants and animals. They have not yet been synthesized. The essential fatty acids are linoleic, linolenic and arachidonic.

LINOLEIC ACID

Linoleic acid is found as a glyceride present in the dry oils of cotton, corn and poppy seeds and others. In animals it is present as the fatty acid of phospholipids and forms neutral fats. Linoleic acid and its esters are absorbed by the intestinal epithelium. They are transformed into arachidonic acid under major activity.

LINOLENIC ACID

Linolenic acid is generally absent in animal fats, and like linoleic acid is present as a glyceride in the dry oils such as linseed oil. It is absorbed by the gastrointestinal tract and transformed into arachidonic acid in the body.

ARACHIDONIC ACID

Arachidonic acid contains four double chains. It is deposited in organic tissue. It is found preferably in animal tissue. It forms part of the phospholipid fraction constituent of lecithin and cephalin and is a component of neutral fats.

It has been isolated from the heart, liver, spleen, suprarenal capsule and brain.

PHYSIOLOGY AND SYMPTOMS OF DEFICIENCY

Linoleic acid is metabolized immediately after it enters the body. It is not stored unless administered in large doses. Linoleic acid has been found in all animals that have been studied as well as in man, as an ester, as a constituent of phospholipids and as a component of neutral fats. Both acids are transformed in the body into arachidonic acid which is more active. In addition to arachidonic acid, other fatty acids are synthesized by the body from linoleic and linolenic acids.

Deficiency produces a type of dermatosis characterized by dryness and cracking of the skin, especially of the ears, hands and eyebrows. Lesions of the lacrimal gland are present and lacrimal hypersecretion begins. Lesions of the kidneys and urinary tract occur. There are disturbances of lactation in the rat, loss of weight and cessation of growth. The symptoms disappear following administration of the essential fatty acids.

ESSENTIAL FATTY ACID REQUIREMENTS

The daily requirements to prevent deficiency are not as yet known.

TREATMENT

Oils containing these essential elements must be ingested. Sources are corn, poppy seed, cottonseed, flaxseed, etc., as well as foods containing lecithin and cephalin, also those sphing myelins which contain these essential fatty acids.

NUTRITIONAL ANEMIA*

Only those anemias produced by deficiency of certain elements necessary for maintenance of normal hematologic conditions will be noted here For purposes of study, the types of anemia may be divided as follows

Nutritional Anemias:
- Anemia due to iron deficiency
- Anemia due to deficiency of the antianemic principle (sprue, pellegra, macrocytic anemia of pregnancy, Addison Biermer pernicious anemia, etc)
- Anemia due to deficiency of vitamin C
- Anemia of the myxedematous type

Macrocytic anemia due to deficiency of the hematopoietic principles:
- Deficiency of the intrinsic factor
  - Cryptogenetic pernicious anemia
  - Pernicious anemia of pregnancy
- Deficiency of the extrinsic factor
  - Sprue
  - Tropical macrocytic anemia
  - Pellagra
- Deficient absorption of the pernicious anemia factor
  - Gastrointestinal disturbances
  - Idiopathic steatorrhea
  - Etc
- Deficient storage of the pernicious anemia factor
  - Cirrhosis of the liver
  - Acute atrophy of the liver
  - Etc
- Deficient utilization of the pernicious anemia factor
  - Achrestic anemia

The following are of particular interest in the tropics

SPRUE OR TROPICAL DIARRHEA

Sprue is a condition observed in tropical or subtropical countries *For* a full discussion, refer to Chapter 60

TROPICAL MACROCYTIC ANEMIA

Hyperchromic macrocytic anemia of tropical countries was first studied in India It develops usually as a complication of such diseases as malaria, syphilis tuberculosis, parasitic infections, etc It has also been described as a nosologic entity not due to infection or other diseases It occurs in both sexes, but Wills found it more frequently in women than in men, particularly as a complication in pregnancy The anemia is produced, generally, by deficiency of proteins fats, and vitamins in the diet

Symptoms —Pallor of the skin and mucosae, vertigo, headache, accompanied by general weakness, glossitis, diarrhea, and edema, are found in this type of anemia

Blood Picture —The blood examination establishes the diagnosis (Hyperchromic macrocytic anemia)

*See also Chapter 68

Treatment.—Crude liver extract is effective but not the purified and concentrated liver extracts. Folic acid, used at present, gives good results. In addition, a diet rich in proteins, fats, and vitamins should complement the treatment. Vitamin B_{12} is also given.

PELLAGRA TYPE OF ANEMIA

Pellagra is discussed in Chapter 62.

ACHRESTIC ANEMIA

Wilkinson and Israels (1935) in India described a macrocytic hyperchromic type of anemia similar to the idiopathic pernicious anemia but which did not respond to treatment with liver extract. This type of anemia is believed to be due to the inability of the body to mobilize and utilize the hematopoietic principle present in the organism. This type of anemia is known as "achrestic anemia."

Symptoms.—The symptoms are glossitis, headache, vertigo, anorexia, asthenia, and loss of weight.

Blood Picture.—The erythrocyte count is 2,000,000 to 3,500,000 or less. The hemoglobin is 60 to 70 per cent. The color index and the volume index are higher than 1.0.* The bone marrow shows megaloblastic hyperplasia.

Laboratory Diagnosis.—The laboratory diagnosis is made by examination of the blood and also by lack of response to treatment with liver extract.

Treatment.—This anemia is chronic, ending in death. Liver extract is not effective.

ANEMIA DUE TO VITAMIN C DEFICIENCY

The anemia due to vitamin C deficiency is a microcytic anemia generally seen in cases of scurvy.

Etiology.—It is due to a deficiency of vitamin C and dietary factors in general.

Pathogenesis.—With symptoms of scurvy and infantile scorbute already described are associated pallor, headache, general malaise, anorexia, asthenia, loss of weight, and pallor of the skin and mucosae.

Hemorrhages of the gums and cutaneous, intestinal, and nasal hemorrhages accentuate and aggravate the anemia.

Blood Picture.—The erythrocyte count is 3,000,000 to 4,200,000 per cubic millimeter or less, in some cases 1,000,000. Hemoglobin is 60 to 75 per cent, although it may be as low as 40 or 50 per cent, with the possible findings of normoblasts and reticulocytes. Leucocytes and thrombocytes are unchanged. In a few cases their numbers decrease but not excessively. Bleeding time and clotting time are normal, as is clot retraction.

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*In the United States the mean corpuscular volume and the mean corpuscular hemoglobin concentration are considered important indicators.

Laboratory Diagnosis—Laboratory diagnosis is made by estimation of the concentration of vitamin C in the blood plus the hemogram

Treatment—Use of a diet high in vitamin C such as lemon juice tomatoes oranges green vegetables etc is associated with large doses of vitamin C accompanied by liver extract preferably parenterally administered and iron

NUTRITIONAL EDEMA

Nutritional edema is the name given to edema produced by decrease or absence of protein elements in the diet The edema is generally produced under conditions during which food is scarce such as wars prison life etc hence the name war edema ' or prison edema "

Symptoms of Deficiency—Edema of varied intensity is the principal symptom In some cases it is mild and is present only in the lower extremities In other cases it extends to the face which presents a typical swelling At times it is generalized with anasarca

The extremities may be extraordinarily infiltrated the abdomen distended with ascites edema of the face infiltrated eyelids sometimes producing difficulty in vision

The edema is of the characteristic type known as ' renal" edema "white' edema soft and cold edema ' symmetrical' edema It may be 2 or 3 weeks before it has become established or it may appear in 2 or 3 days It is more pronounced in the more dependent parts of the body for example in male patients the scrotum is distended increased in size and acquires a porcelain like appearance in some cases even showing fissures through which secondary infection occurs After a time symptoms of vitamins B_1 and PP deficiency are added to the symptoms of edema

In some cases motor and psychic disorders changes in circulation and hepatic changes accompany the edema Anemia is usually present and in addition there are photophobia and conjunctival congestion Dental disorders are also usually observed leading to dystrophy Other symptoms are anorexia and low arterial tension with tachycardia and cardiac murmurs as well as electrocardiographic changes characterized by disappearance or slight inversion of the T wave due in part to aqueous imbibition of the heart muscle and to deficiency of vitamin B_1 associated with protein deficiency

Some patients show sensory alterations such as somnolence obnubilation depression etc while others maintain a normal state Cutaneous and tendinous reflexes are weakened

Protein Requirements—A sufficient quantity of protein is required to prevent nutritional edema as well as other metabolic changes related to protein deficiency and which may hasten death

In nurslings the optimum quantity is 1 5 Gm per pound of body weight In adults the amount varies from 20 to 130 Gm daily although with proteins of the first class 30 to 40 Gm may be considered as minimum In a diet of 3 500 calories at least 50 gm should be proteins of the first class such as those found in milk eggs and meat with 50 Gm of proteins of the second

class such as vegetable proteins In pregnancy lactation and growth the quantity of protein intake should be increased to maximum In pregnancy, *the quantity should be 1 5 Gm per kilogram of body weight*

Proteins make up 10 to 15 per cent of the calories in the diet The average amount of protein which an adult should ingest in order to prevent hypoproteinemia is 100 Gm per day

Laboratory Diagnosis—The amount of proteins in the serum is determined by gravimetric refractometric or colorimetric methods

The refractometric method uses the Abbee or the Pulfrich refractometer which is a rapid method, but it estimates the proteins as a whole without specifying the quantities of each

The colorimetric methods determine the quantity of serum albumin serum globulin and fibrinogen so that the albumin globulin ratio may be established This is very important in the study of edema in general In this particular case it is important in the study of deficiency

There are several methods such as those of Andersch and Gibson Greenberg and others The Kjeldahl method or the oxalic catalysis give excellent results

The normal amount of protein in the blood is total protein 7 1 Gm per 100 c c of plasma, fibrinogen 0 27 Gm to 100 c c of plasma serum albumin 4 1 Gm to 100 c c of plasma serum globulin 2 7 Gm to 100 c c of plasma The albumin globulin ratio is 1 1 5 In serum the amounts are albumin 5 Gm to 100 c c of serum globulin 2 2 Gm to 100 c c of serum albumin globulin ratio 1 2 2

Blood examination alone will not establish a diagnosis of hypoproteinemia due to nutritional deficiency since while it indicates the protein state of the blood it does not indicate whether the condition is due to renal or to nutritional disturbances or to other organic conditions Examination of the urine is decisive since albuminuria and renal sediment typical of hydropathic nephropathy *especially hematuria are conclusive indications of renal edema* whereas, in nutritional edema these changes are lacking The sediment consists of cylindroids of mucus specific gravity is high 1 020 to 1 025 or more the reaction is acid urea and chlorides are normal or above normal and the phosphates and sulfates are also above normal

Treatment—Treatment consists primarily in diets high in proteins In nurslings albuminous milk is given every 3 hours in older children soups and broths meat paste green vegetables and abundant animal proteins in adults beef veal pork cow's milk goat's milk green vegetables grains such as beans chick peas peas lentils etc As dessert fresh fruits such as oranges grapefruit pears etc are given

In serious cases blood plasma transfusions are given in 200 to 500 c c quantities at a time If there is associated anemia whole blood is used 200 to 400 c c at a time with successive transfusions if required

Diuretics such as the following should be used hypertonic solution of glucose 30 to 50 per cent intravenously caffeine ammonium chloride calcium chloride, strontium and calcium lactate

Vitamins B_1 and B_2 should be administered as well as A and D therapeutic doses in relation to the condition of the patient Cardiac to such as Coramine in high doses and caffeine should be used

Liver extract should be used as a coadjuvant In treatment of nu tional edema care should be taken to observe any other cause responsible the edema since not only is the low intake of proteins responsible for [illegible] but in some cases of excessive loss the intense destruction of prot or [illegible] formation of proteins are the causes of hypoprotein edema

MINERAL DEFICIENCIES

Only the more important of these mineral deficiencies such as calci [illegible] iron and iodine will be considered

CALCIUM

[illegible] presents 2 per cent of the body weight, 98 per cent of this [illegible] in the skeleton

Symptoms of Calcium Deficiency—Among the fundamental sympt [illegible] nervous and muscular hyperexcitability, with spasmophilia [illegible] of calcium in the plasma as well as to decreased ionized calci [illegible] occurring when phosphates and citrates are increased Alk sis [illegible] by excessive ingestion of bicarbonates or in loss of gastric ju by vomiting causes decreased calcium with symptoms of tetany Deficien also are apparent in the blood coagulation process with excessive loss of bl in traumatic wounds as a result of the increased coagulation and blee times Deficiency of calcium is apparent in the process of coagulation of m

Disturbances in water metabolism and in the acid base equilibrium produced Symptoms of hypocalcemia are disorders of ossification lack growth osteoporosis defective tooth formation digestive disturbances ste ity and premature death

Foods Which Contain Calcium—Foods which contain calcium are fun mentally milk which contains 1 4 per cent calcium cheese 5 to 10 per ce raw green vegetables and some natural waters which contain a high prop tion of calcium

Calcium Requirements—Sherman considers the calcium requirements be 0 45 Gm per day but since the process of absorption varies he rec mends administering a double quantity that is 0 8 Gm in adults in chil between the ages of 1 and 10 years 1 Gm , from 10 to 12 years 1 2 Gm , fr 13 to 15 years 1 3 Gm and from 15 to 20 1 4 Gm daily In pregnancy lactation the quantity of calcium to be taken is greater, 1 5 Gm daily recommended for pregnant women and 2 Gm in lactation

Laboratory Diagnosis—The normal calcium content of the blood is to 12 mg per 100 c c of plasma Diffusible calcium is 5 to 6 5 mg per c c of plasma and nondiffusible calcium is 4 to 5 mg per 100 c c of plas Diagnosis of calcium deficiency is made by estimation of total blood calci

diffusible and nondiffusible using any of the standard methods among which may be cited that of Kramer and the modified method of Kramer and Tisdal also the method of Clark and Collip

Treatment —Give the patient diets rich in calcium such as milk cheese and raw vegetables calcium gluconate orally in doses of 11 02 Gm calcium lactate in doses of 7 2 Gm or calcium chloride in doses of 0 10 Gm every 3 hours orally Calcium gluconate is used intravenously in doses of 5 to 10 c c containing 10 or 20 per cent of the gluconate Vitamin D is used to permit fixation and utilization of the ingested calcium

PHOSPHORUS

Phosphorus is found in the human body in quantities varying from 450 to 700 Gm 70 to 80 per cent of which is present in bones and teeth in combination with certain substances but principally combined with calcium Phosphorus is eliminated by the kidneys about 60 per cent normally being found in the urine

Symptoms of Deficiency —Deficiency of phosphorus results in rickets in the child and osteoporosis or osteomalacia in the adult with retardation of growth and usually a poor organic state with disturbances eventually leading to death Hypophosphoremia that is blood phosphorus below normal has been noted Blood phosphorus is found in the form of inorganic and organic phosphorus Organic phosphorus occurs in three forms ethereal lipid and nucleic

Decreased phosphorus is observed in rickets Calcification does not take place and bones bend easily due to diminished absorption of phosphorus In osteomalacia bones become soft and deformed especially the pelvic bones

Foods Which Contain Phosphorus —Foods which contain phosphorus are

Milk	Beef muscle
Cheese	Beef liver
Butter	Eggs
Cereals	Vegetables

Phosphorus Requirements —In the adult 0 88 Gm of phosphorus may be administered daily as a maintenance dose But the diet should contain 1 35 to 1 40 Gm per day In pregnancy and lactation the dose should be increased to 2 5 and 3 0 Gm daily Growing children need a greater quantity of phosphorus at 3 years they require 80 mg per kg of weight at the age of 16 years 32 mg per kg adults require 12 mg per kg of weight daily The ratio of phosphorus to calcium in the diet should be 2 1 and no less than 1 1

Laboratory Diagnosis —The normal quantity of phosphorus is 40 mg per 100 c c of blood It is present principally as organic and inorganic phosphorus

Inorganic phosphorus is normally present in the amount of 3 to 4 5 mg per 100 c c of blood plasma in adults and 4 to 6 mg per 100 c c of plasma in children Phosphatase is an enzyme which hydrolyzes the monophosphoric

esters, with liberation of phosphoric acid It is found in all cells and body fluids According to whether its action develops in an acid or alkaline pH, we speak of "acid" or "alkaline" phosphatase Alkaline phosphatase is found in greater quantities in such organs as intestines, kidney, liver, bones and teeth Acid phosphatase is found in liver, kidney, prostate, and erythrocytes

Tests for inorganic phosphorus can be made by several methods, among which are the methods of Kuttner and Lichtenstein Bell and Doisy, Fiske and Subbarow, and others All figures below the normal limit indicate hypophos phoremia and establish a direct diagnosis of phosphorus deficiency

"Alkaline' phosphatase is determined by the methods of Kay, Bodansky, or King and Armstrong "Acid" phosphatase is determined by the Gutman method One and five tenths to 4 0 units are considered normal for "alkaline" phosphatase and 4 Bodansky units are considered normal for "acid" phos phatase The normal "alkaline" phosphatase in children is 5 to 15 Bodansky units

Treatment—In cases of phosphorus deficiency, food rich in this mineral should be administered such as milk cheese, beef muscle, liver, vegetables cereals eggs, etc in addition to the oral administration of sodium and potas sium phosphate in the form of glycerophosphates Phospholipids and phos phoglycerates are useful in treatment

IRON

Iron is essential for maintenance of life, being a constituent of the mole cule of hemoglobin which in turn, transports oxygen and carbon dioxide in the process of respiration The amount of iron in the body is about 3 Gm 65 per cent of which forms part of the hemoglobin, the rest being distributed in the liver spleen and bone marrow, and in the remainder of the organism

Symptoms of Deficiency—Hypochromic anemia occurs as a result of iron deficiency

Foods Which Contain Iron—Foods which contain iron are

Beef liver	Beef muscle	Egg yolk
Pork liver	Vegetables	Legumes

Iron Requirements—Daily requirements are from 10 to 20 mg for men and from 20 to 25 mg for women, an average dose of 12 mg for men and 15 mg for women may be given In pregnancy and lactation the daily dosage should be increased, children require 6 mg daily in the first year, gradually increasing to 15 mg by the age of 15 years

Laboratory Diagnosis—Iron deficiency can be determined indirectly by estimating the hemoglobin concentration Iron in the circulating blood can be determined directly by the method of Wong The normal amount in the male is 42 mg per 100 c c of plasma, in the female, 38 mg per 100 c c of plasma

Treatment—Daily doses of the ferrous salts, such as ferrous chloride orally, are advisable, parenteral injections containing 16 to 35 mg of iron may be used, and food with high iron content, such as meat, vegetables legumes, egg yolk, liver, etc should be eaten

IODINE

Iodine is a constituent of thyroxin and numerous iodine compounds formed by the thyroid gland The principal compound formed by the thyroid gland is thyroxin It was extracted from the thyroid gland by Kendall in 1914 In 1924 and 1926, Harrington determined the structural formula, and in 1927, with Barger, prepared it synthetically

Symptoms of Deficiency—Iodine deficiency results in hypertrophy of the thyroid gland Hypertrophy of this gland develops first as a consequence of hypertrophy of the cells, later cellular hyperplasia occurs In some cases, the gland may be overwhelmed with resulting atrophy

Iodine Requirements—Generally, iodine taken in food and water is sufficient to prevent deficiency In regions where it is not present in the water, so called "goiter zones" result, as, for example, in the Swiss Alps, northern France, Derbyshire in England, Himalayas in Asia, and in the Great Lakes region of the United States, and in parts of the Rocky Mountain region It is to be noted that iodine in very small quantities is found as a constituent in the water in cold regions far from the sea

Treatment—Iodine is used in the form of solutions of iodized iodine giving 2 drops per day until a dose of 60 drops has been reached Thyroxin may also be used administered orally

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CHAPTER 60

SPRUE

RAMÓN M SUÁREZ

Synonyms—Psilosis tropical diarrhea aphthae tropicae Ceylon sore mouth Cochin China diarrhea

DEFINITION

When sprue syndrome is fully developed it is characterized by glossitis flatulent diarrhea with fatty frothy stools which produce burning in the rectum marked loss of weight and a macrocytic hyperchromic anemia

The "marked tendency to remissions" of which most authors speak is rarely if ever seen in practice Unless adequately treated the disease progresses gradually to complete prostration inanition and death On the other hand relapses are rather frequently seen in patients who have discontinued the prescribed therapy or who have been unable to follow the recommended diet

GEOGRAPHIC DISTRIBUTION

For many years sprue was supposed to be limited to the tropical and subtropical latitudes Thaysen (1932) reported the first cases of the so called "nontropical" sprue in northern Europe Shortly afterward many such cases were being reported from the United States of America not only from the southern but also from the northern states

We have seen no less than 400 cases of sprue and not over 20 cases of Addisonian pernicious anemia in Puerto Rico during the last 20 years a ratio of 20 sprue patients for 1 of pernicious anemia The syndrome is easily confused clinically with several other diseases and hematologically it is indistinguishable from pernicious anemia Undoubtedly some cases of true pernicious anemia occurring in the Tropics have been erroneously diagnosed as sprue especially when they have exhibited gastrointestinal manifestations and loss of weight

The sprue syndrome has been reported from the Philippine Islands French Indo China South China Java the Straits Settlements Ceylon India Mauritius the Fiji Islands the West Indies Central America Guianas Queensland Iraq Egypt and Malta The British Commonwealth is said to be the largest reservoir of nutritional macrocytic anemia (Editorial 1946) Authentic records of sprue are rare in North and Central Africa Palestine and Arabia Recently De Figueredo (1941) reported a case in Brazil where it was supposed not to exist

HISTORY

The sprue syndrome has long been known to medical science having been originally described by J Ketelaer (1669) who published *De Aphthis Nostratibus Seu Vulgarum Sprouw* The name "sprue" was applied therefore to the aphthous stomatitis accompanied by the passage of voluminous stools which occurred among the Belgians Hillary

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CHAPTER 60

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(1766) is credited with the first clear description of the disease, his observations being based on clinical experiences during a 6 year residence in the Barbados (1753 1759) Real scientific interest in this disease may be said to date from the writings of Sir Patrick Manson (1880) in China and of Van der Burg (1880) in Batavia Van der Burg's contribution was based on the study of 1,407 cases during his 30 years' experience in Java, but Manson was probably the first to suggest that "bad or insufficient food" was of major importance in the causation of sprue In more recent years, especially in America, a renewed interest in the disease has undoubtedly been brought about by the studies, observations, and contributions of Ashford in Puerto Rico

To those who believe that celiac disease and sprue are one and the same disease, we may say the history of the syndrome goes back to the second century A D, when Caelius Aurelianus and Aretaeus of Capadocia (cited by Gibbons, 1889) described an illness characterized by flatulence, eructations, "*heavy pain of the stomach now and then, as if from a puncture,*" emaciation, paleness, and muscular weakness (Abdominal pain as "if from a puncture" is rarely, if ever, observed in sprue)

Gee (1888) seemed to recognize that adults as well as children were similarly affected and considered celiac disease as identical with the endemic *diarrhea alba* (tropical sprue) of India Gibbons (1889) considered the condition as entirely different from sprue and believed it to be the result of a functional disturbance Herter (1908), apparently unaware of previous work on the subject, described 5 cases of celiac disease in dwarfed children under the name of "intestinal infantilism," and Heubner (1923) described the occurrence in children of what he termed "severe intestinal insufficiency," emphasizing the intestinal malabsorption as the fundamental cause

In recent textbooks of pediatrics, such terms as "chronic intestinal indigestion," "fat intolerance," "chronic digestive insufficiency," "intestinal infantilism," "schwere chronische Ernahrungstorung jenseits de Saugling Alters" are used to describe the same condition

From an historical point of view, it is interesting to recall that liver therapy was used by Chinese physicians in the treatment of sprue hundreds of years before the epoch making discovery of Minot and Murphy (1926) on the specific effect of liver therapy in pernicious anemia

EPIDEMIOLOGY

Sprue is a regional rather than a climatic disease, it pre eminently affects Europeans Dark skinned people are less likely to acquire the disease In our study (Suarez, 1938, 1938a) of 150 cases, 121 were white, 26 were mulattoes, and only 3 were Negroes The disease is occasionally seen in the Mongolian race, in the Malayans, and in Indians

The disease is apt to occur in one or more members of the same family Our experience has shown that sprue or pernicious anemia had often existed in one of the patient's parents, usually the mother In many instances, sprue has developed in husband and wife, it is probable, as Manson Bahr states, that both had been exposed to the same influences The female sex appears to be more likely to develop the disease than the male Atmospheric temperature does not influence the incidence of the disease, for it originates at high altitudes in Ceylon *and in the Himalayas, where the climate resembles* more that of Europe

Sprue and pernicious anemia have so many features in common that it has been repeatedly suggested (Suárez, 1931) that the former may constitute a geographic variety of the latter It is now becoming clear that pernicious

anemia also exhibits certain geographic peculiarities being especially p to affect people of the northern hemisphere and extremely rare or absen native tropical races

It may well be that besides a distinct regional incidence sprue and p nicious anemia as well as Cooley s anemia and sickle cell anemia may exhi a distinct racial incidence The incidence of sprue in Puerto Rico and el where has diminished in frequency and severity during recent years Ma son Bahr believes that this possibly depends to some extent on improve hygienic conditions We favor the idea that the more liberal use of liver e tract accounts for it

Sprue is a disease of the young and middle aged In our series of 15 ases 50 or ⅓ were under 40 years of age The youngest patient was 9 and he oldest 84 years of age There were 7 cases in the age group of 9 to 20 ears 43 in the age group of 21 to 40 79 in the age group of 41 to 60 and 21 itients were over 60 years old The youngest patient reported by Rodriguez Molina (1941) in a series of 100 was 12 years at the University Hospital the youngest in a series of over 120 cases was 10 years of age

The general appearance of a few of our older patients with premature graying of the hair and lemon tint to the skin renders them indistinguish able from pernicious anemia

ETIOLOGY

It is said that the etiology of sprue is still obscure To be more ex act we should say that it remains unknown but that the recent experience with folic acid has brought us closer to its mechanism There have been many theories offered from time to time to explain the etiology of the disease Most theories have been definitely discarded but some are still holding

1 The theory that sprue is caused by a *yeast (monilia)* has been abandoned

2 The theory of *calcium deficiency* was presented by Scott who was impressed by the similarity between many of the symptoms of sprue such as tetany cramps loss of weight and edema and those of disordered calcium metabolism In the tropics at least in Puerto Rico evidence of altered calcium regulation is meager In spite of our low calcium intake (the diet of the Puerto Rican *jibaro* [country resident] contains 0 09 Gm of calcium per 100 Gm as compared with 0 35 Gm in the continental United States diet) we have not observed evidences of abnormal calcium metabolism. No doubt that the abundant sunlight present throughout the year in Puerto Rico can explain our clinical and biochemical findings Scott s hypothesis of a disordered calcium metabolism can therefore be discarded also

3 The theory of *infection* has had and still has many enthusiastic advocates Against the infection theory are the afebrile course in sprue and the absence of leucocytosis and of anatomic pathologic evidences of bacterial invasion

In Manson Bahr s experience, there is considerable amount of evidence of a close association between sprue and amebic dysentery and other intestinal diseases We have seen as it will be pointed out later the coexistence of sprue and other intestinal diseases such as schistosomiasis lymphogranuloma venereum and ulcerative colitis We have not observed its association with amebic dysentery, but there is no reason why both diseases should not coexist in Puerto Rico as elsewhere except for the relatively low incidence of amebic dysentery in the Island

4 Pock-Steen (1941) presents a very hypothetical theory and a series of tables to explain the etiology of sprue on 2 main factors *histamine intoxication* and *loss of vitamin B₂* According to his view, there are "incipient sprue," "prosprue," and "anatomic sprue," and he adds that climatic causes produce an adrenal insufficiency from which result, on the one hand a histamine toxicosis, and, on the other, activation of phosphorolyzing ferments the latter by interfering with resorption of vitamins, fats, and glucose, leads to deficiency of vitamin B₂

5 The theory of *failure of the anterior pituitary* secretion is the latest and most original contribution of Vedder (1940) to tropical medicine

The author postulates that the failure of absorption of fat, sugar, salts, and vitamins from the small intestine is due to a functional failure of anterior pituitary secretion, precipitated in some individuals by tropical service He admits, however, that no proof of this has been offered

The severe state of malnutrition observed in sprue is comparable to Simmonds' cachexia The 2 conditions may be considered similar only when looked at superficially from a distance Vedder speaks of the hypochromic anemia of sprue which, in our experience and in that of most students of the disease, is rare

6 One of the latest hypotheses to explain the etiology of sprue has been offered by Manson Bahr (1941) He calls it "jejuno ileal inefficiency" This newer concept may be summarized by stating that sprue is the result of dysfunction of some specialized cells of the gastrointestinal tract in the same manner that the theory is generally accepted for pernicious anemia with respect to the pyloric and Brunner's glands of the duodenum In pernicious anemia the dysfunction is complete and permanent, in sprue the dysfunction is apparently temporary and complete cure is frequently observed without the need of continuous treatment

Although there is no direct microscopic evidence many observers have pointed out that lack of absorption from the small intestine is the principal defect in sprue Bennet and Hardwick (1940) discuss the results of failure of function of the small intestine, which produces a syndrome of steatorrhea, tetany, and macrocytic anemia, with stomatitis and pellagrous skin lesions Within this syndrome fall celiac disease (idiopathic steatorrhea) and tropical sprue That there is impaired absorption from the small intestine is also suggested by the flat glucose and flat blood fat curves, by the glycine tolerance test, and by the study of the relation of phosphorus to fat

Evidence in favor of the theory of jejuno ileal insufficiency is provided by gastrocolic fistula Such a case is described by Hanes and Reiser (1940) in a man 46 years old, who developed the complete sprue syndrome with steatorrhea (56 per cent total fat), macrocytic anemia and tetany Following laparotomy, which restored the normal continuity to the bowel complete recovery ensued

According to this most attractive theory, "gastroduodenal inefficiency," with its dysfunction of the pyloric and Brunner's glands of the duodenum, is the cause of primary pernicious anemia subsequent to partial gastrectomy The "jejuno ileal inefficiency" is the cause of primary sprue, tropical and nontropical, of secondary sprue or sprue artificially produced by gastrojejunocolic fistula, gastrojejunostomy and short circuit, by neoplasm of the small intestine mesenteric tuberculosis, and lymphadenoma It is also the cause of celiac disease, congenital absorption defect in the small intestine proceeding to idiopathic steatorrhea in adults Furthermore, according to this hypothesis, "ileocecal inefficiency" is the cause of pellagra and of secondary pellagra artificially produced by damage to the ileum or more often to the large intestine by chronic bacillary dysentery, alcohol, and by surgical intervention

The theory appears to be an interesting anatomic distribution of pathology which does not go very far into the real underlying cause Assuming that it is correct, that there exists a "jejuno ileal inefficiency" in sprue, what is the cause of the abnormality insufficiency, or inefficiency of the small intestine?

Manson Bahr himself admits that there is no direct microscopic evidence to account for the lack of absorption from the small intestine in sprue On the other hand the

work of Rodríguez Olleros (1938) and Hernández Morales (1944) at the School of Tropical Medicine of Puerto Rico has shown that atrophic gastritis and atrophic rectosigmoiditis are found in sprue probably as frequently as atrophic gastritis is encountered in pernicious anemia and rectosigmoiditis in pellagra

7 Verzár's (1936) theory that the underlying physiologic defect in sprue is a breakdown in the *phosphorylating mechanism of absorption*, due to a defect in adrenal cortex activity, was investigated by Hanes and Reiser There is evidence that the sprue patient is capable of metabolizing glucose normally, after it is in the blood Consequently, the delayed fall in the serum phosphorus after glucose ingestion can be explained solely on the basis that the sugar reaches the blood stream very slowly and is then as slowly absorbed. This does not support Thaysen's theory that the low blood sugar curve is due to abnormally rapid assimilation of the absorbed glucose by starved tissue Sprue patients do not exhibit the normal fasting diurnal variation in phosphorus excretion, and after ingestion of olive oil there is an increased urinary phosphorus excretion, whereas in normal persons, there is a decrease with no significant change in serum inorganic phosphorus These findings, as well as the delayed changes in respiratory quotient after oil and glucose meals, prove to the authors the slow rate of intestinal absorption

8 Stannus (1942) brings forward another theory as to the etiology and pathogenesis of sprue The primary failure is one of phosphorylation not due, as suggested by Verzár, to lack of adrenal hormonal control but to *defective enzymatic action*

Evidence is adduced in favor of a theory, based upon the "partition" hypothesis, that predicates for unsplit (neutral) fat and for fatty acids a different mode of absorption from the intestine, a route after absorption, a composition during transport, a destination, and a role in the bodily metabolism

(a) The deficient absorption of fat is primarily limited to loss of power to absorb the fatty acid moiety and cholesterol

(b) There is no loss of power to absorb neutral fat (glyceride), but there is deficiency of neutral fat absorption due secondarily to nonabsorption of fatty acid

(c) There is also a primary loss of power to absorb glucose which results in a low flat oral blood sugar tolerance curve, glucose no longer being selectively absorbed by an active process but by diffusion only

(d) The same is true of glycerol formed by the splitting of neutral fat

(e) The loss of power to absorb fatty acid glycerol, and glucose is probably due to failure of phosphorylation They are all substances, as opposed to many others, which require to be phosphorylated on absorption by the intestinal mucosa

(f) Neutral fat is normally absorbed as a finely dispersed emulsion and does not require to be phosphorylated Failure of absorption is secondary to nonabsorption of fatty acid

(g) Fructose (levulose) is normally absorbed without phosphorylation and utilized by the sprue patient as by the normal subject

(h) Loss of calcium to the body is due to "fixation" by the fatty acid in the bowel, with the formation of insoluble soaps

(i) Loss of phophorus is due to defect in phospholipid formation resulting from failure of phosphorylation

(j) The enzyme, or enzymes, which catalyze phosphorylation—the "carriers" of phosphoric acid—probably have, as the active part of the molecule, coenzymes embodying some member or members (identified or unidentified) of the vitamin B_2 complex

(k) The nature of the fatty acids in the diet may be a factor in determining the geographic distribution of the disease

Among the identified members of the vitamin B_2 complex Stannus (1942) mentioned riboflavin, nicotinic acid, pyridoxine, and choline but failed to mention folic acid, which is effective in sprue The mechanism of its action is as yet undetermined.

9 *Dry wood inhabiting termites* There has been for many years a prevalent belief in Ceylon that continued residence in so called "dry rot bungalows" is a predisposing factor in the causation of sprue

This problem was thoroughly studied by Jepson (1933), who found that the portion of buildings most commonly infested by these termites are the roof timbers, and that it is relatively frequent for the fecal pellets of these insects to fall on the articles of food He also found that, in general, the world range of sprue and these termites is very similar His study suggests that the ingestion of the fecal pellets of the dry wood inhabiting termites in food might be responsible, directly or indirectly, for the causation

Puerto Rico is one of the countries in which both the disease and these insects are common, but we have been unable to determine any direct relationship of cause and effect between the two except for the fact that the people who live in old wooden houses where termites are more common, usually belong to the low income group and consequently are more likely to receive an unbalanced diet

10 The concept of a *constitutional* or inherited defect in sprue, as in pernicious anemia, is difficult to evaluate, but we cannot escape the conviction that the fundamental constitution of the patient plays a role in the development of the disease, it is an accepted fact that there is a definite racial predisposition

11 Infectious diseases, debilitating influences, pregnancy, and many conditions that are associated with disorders of digestion or of assimilation of food may serve as *contributory* or *conditioning* factors

12 The concept of a *deficiency state* in the etiology of sprue is one of the theories that has been able to withstand prolonged investigation In favor of this theory is the fact that cases of sprue have been treated successfully with different diets marmite soup, meat diet, milk and strawberry diets, etc Before vitamins were in vogue, Ashford used to consider an "unbalanced diet" as an important causative factor in sprue A vitamin deficiency hypothesis, founded upon experimental work in monkeys, has been suggested by McCarrison The theory rests also upon the similarity, in some respects, between sprue, pellagra, and idiopathic steatorrhea, and upon the frequent observance of secondary vitamin deficiencies in the fully developed cases of sprue

While working in Puerto Rico, Castle, Rhoads and their collaborators (1933) confirmed the belief that deficient diets frequently antedate the onset of clinical sprue They demonstrated that feeding of the vitamin B complex, in the form of autolyzed yeast, produces reticulocyte crises and improvement of the blood picture in certain cases The intrinsic gastric factor was found lacking in other instances, and some of the more severe or advanced cases showed an apparent defect in absorption from the intestinal canal Castle states "It is probable that the usual type of diet is such as to favor a diminished consumption of some of the known sources of the extrinsic factor, such as meat eggs, and whole wheat grain During recent years a deficiency of vitamin B_1 has been blamed often for the production of sprue It is a fact that many sprue patients have been relieved of their symptoms by the ingestion of marmite soup or of autolyzed yeast A few cases of pernicious anemia have been successfully treated by Wintrobe with huge doses of yeast There is no observable difference between the oral lesions of sprue and those of a fully developed case of pellagra "

A suggestive link in the chain of evidence of the relation between vitamin deficiency and sprue has been supplied by Miller and Rhoads (1935) who, by feeding a deficient diet, produced a state in hogs which they believe is closely analogous to the human sprue syndrome

13 *Folic acid* The one greatest contribution to a clearer conception of the etiology of sprue has been supplied by the recent work of Spies and his collaborators in Cincinnati, Birmingham Cuba, and Puerto Rico They have conclusively proved that folic acid (*Lactobacillus casei* factor) (Spies et al, 1945, Vilter et al, 1945, Spies et al, 1946, Spies et al, 1946a) is capable of producing a marked clinical improvement and hematologic response not only in Addisonian pernicious anemia but also in sprue and in the macrocytic anemias of pellagra and of pregnancy

DIET AND PREVALENCE OF SPRUE

After discussing the diet of 63 of the 92 sprue cases studied Castle and his collaborators (1932) in Puerto Rico stated "It is probable that the usual type of diet is such as to favor a diminished consumption of some of the known sources of the extrinsic factor such as meat eggs and whole grain cereal"

According to Asmayer the diet of the Puerto Rican country resident is low in vitamin A in calcium in phosphorus and in fats but is apparently adequate in proteins carbohydrates and iron We consider that it has an excessive amount of carbohydrates The protein content of the diet of the Puerto Rican is made up chiefly of vegetable proteins of low biologic value

Robinson's investigations* proved that the diet of the low income group is low in calories proteins calcium vitamin A riboflavin and niacin and probably adequate only in iron and ascorbic acid The lowest values were obtained for calcium vitamin A and riboflavin

In 1938 we said "This most inadequate diet has been taken steadily since childhood by many of the sprue patients true enough but it has also been taken by nearly all those suffering from hookworm infestation Yet both clinically and hematologically the hookworm anemia differs from that of sprue The former is invariably hypochromic microcytic or normocytic the latter is typically macrocytic Diet therefore important as it may be far from explains the whole story"

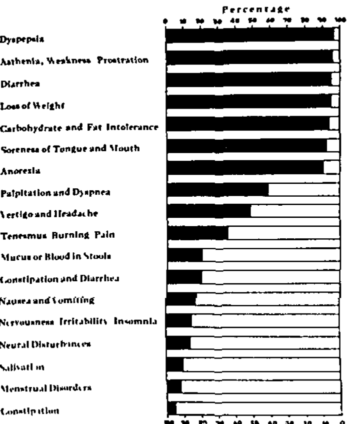
CLINICAL PICTURE

The sprue patient as we see him in Puerto Rico is usually a young or middle aged white individual who complains of a persistent diarrhea and general weakness There is also anorexia flatulent dyspepsia and a sense of epigastric fullness History shows that he has been sick for a number of months progressively becoming worse Physical examination reveals a pale weak emaciated patient His skin is dry and wrinkled occasionally hyperpigmented but rarely will it show purpuric spots on the forearms and ears The sclera will reveal a slight subicteric tint His frontal teeth may be missing and all the others in addition to the gums will be in poor condition The tongue will be inflamed showing crops of minute whitish painful vesicles with a fiery red border in early cases The late cases will have a beefy tongue with atrophy of both the filiform and fungiform papillae—the typical atrophic glossitis of pernicious anemia

On physical examination the heart and lungs will be found negative but the abdomen somewhat distended with dilated intestinal loops The liver and spleen are not palpable the glandular system will be normal In the majority of cases there will be no evidence of central nervous system involvement although many will complain of cramps in the legs and of emotional instability

Stools are frequent copious pale fermenting and foul smelling Anywhere from 3 to 20 bowel movements a day is the usual number

*Personal communication



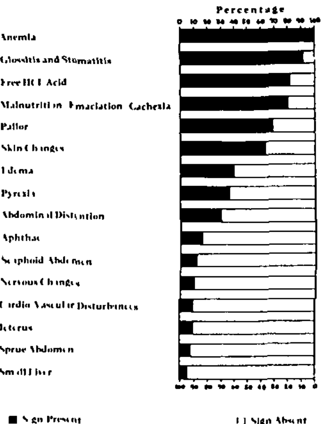


Fig 443.—Diagram showing the relative frequency of the symptoms and signs in sprue (Courtesy of Rodriguez Molina.)

The majority of patients will have a history of a prolonged ill balanced diet In some toothless individuals who have spontaneously limited their diet to liquid or semisolid foods we have observed typical and rather severe cases of acute sprue

It used to be said that sprue was a disease of the upper well to do classes We cannot subscribe to this statement In our experience the disease is as frequent if not more frequent in the low income groups of people

The onset of the disease is usually insidious but the course may be sub acute or chronic The former progresses for 1 or 2 years but the latter may be present for a period of 10 to 15 years

At the time the sprue patient applies for medical treatment laboratory examination will usually reveal the presence of a macrocytic hyperchromic anemia a megaloblastic bone marrow a flat glucose tolerance curve and either a hypochlorhydria or a histamine resistant achlorhydria in the gastric secretion

We have given the usual classical picture of sprue as we have seen it in a subtropical climate Many authors have given artificial descriptions of various types of sprue Some are called protopathic sprue which is the type usually found relatively easily diagnosed and which may also be termed complete sprue Other types are the incomplete or gastric sprue in patients who do not suffer from diarrhea and the intestinal type in which the mouth is not eroded and there is little or no dyspepsia but the stools are liquid copious pale and frothy

Patients who have received only small doses of liver are likely to show a normal tongue and mouth in the presence of a persistent and at times troublesome diarrhea Manson Bahr has also described the type sprue without diarrhea occurring in cases wherein the sore mouth the dyspepsia and the diarrhea subside under treatment but the wasting continues the stools remain phenomenally copious and the patient gradually dies of inanition We have yet to see such a case

If to the various types of sprue just mentioned we would add as suggested by Thaysen and Hanes the so called infantile sprue or celiac disease dwarfism with or without bone deformities osteomalacia and idiopathic steatorrhea there could not be such a thing as clinical picture of sprue '

DIAGNOSIS

A diagnosis of sprue based exclusively on clinical grounds is prone to error A combination of glossitis anemia loss of weight and diarrhea with or without steatorrhea may be observed in various conditions unrelated to sprue We have seen cases of simple achlorhydric anemia hookworm anemia syphilitic glossitis intestinal and peritoneal tuberculosis chronic enteritis and colitis neoplastic diseases and cases of Addisonian pernicious anemia diagnosed and treated as sprue On the other hand in our own series we have proved cases of sprue in which the intense pigmentation and low blood pressure strongly suggested Addison s disease

The help of the laboratory is essential to establish a definite diagnosis of sprue As already mentioned a macrocytic hyperchromic anemia a megaloblastic bone marrow a flat glucose tolerance test a low or absent free hydrochloric acid in the gastric secretion an increase in fat content of the stools and roentgenologic evidences of deficiency states would serve the purpose

DIFFERENTIAL DIAGNOSIS

Pernicious Anemia

The differential diagnosis between sprue and pernicious anemia is not so easy as one might be led to believe by reading some of the standard text books on tropical medicine We quote from one of them The anemia of sprue greatly resembles that of true Addisonian anemia though normoblasts are rare in the blood of sprue and megaloblasts do not occur " We do not know of any means by which the blood of sprue could be distinguished from that of pernicious anemia moreover the bone marrow pictures of the 2 diseases are indistinguishable

The following may help in the differentiation (1) the marked degree of emaciation present in sprue as contrasted with the slight loss of weight and apparent good nutrition in pernicious anemia (2) the flat glucose tolerance curve in sprue and the normal curve in pernicious anemia (3) the roentgenologic evidence of deficiency often observed in sprue and absent in pernicious anemia (4) the high fat contents in the stools of sprue patients with normal stools in pernicious anemia (5) the frequently enlarged or palpable spleen in pernicious anemia smaller in size or normal in sprue The complete and persistent histamine resistant anachlorhydria and the signs and symptoms so characteristic of Addisonian anemia of combined cord degeneration are of no practical importance in the differential diagnosis as they may be observed also although less often in sprue

Castellani s rhamnose test intended as a gauge of absorption of monosaccharide sugars from the intestine is considered by Amalfitano (1939) to be diagnostic of sprue if it fails to appear in the urine

Rodriguez Olleros and Hernandez Morales (1940) claim that sprue and pernicious anemia may be differentiated by the test designated as *gastric chromoscopy* which follows

After a 12 hours fast the patient is given 0 2 Gm of caffeine in 300 c c of water colored with 2 drops of a solution of methylene blue to stimulate gastric secretion

The result is analyzed after the stomach has been emptied and then 5 c c of a 1 per cent neutral red solution are injected into the gluteal region If the gastric contents are found to contain no free hydrochloric acid histamine is given subcutaneously at the same time

Thereafter the gastric contents are withdrawn every 5 minutes until the red coloration appears and the interval between the injection and the appearance of the dye in the stomach is noted

The authors conclude that the elimination of the neutral red by the gastric mucosa in cases of sprue is more rapid (time varied from 5 to 40 minutes)

than in those cases with the same degree of hydrochloric acid secretion but suffering from a condition other than sprue In a case of pellagra and another case of pernicious anemia the dye failed to appear in the gastric contents

Chronic Pancreatitis

The differentiation from chronic pancreatitis may occasionally present difficulties In chronic pancreatitis the neutral fats predominate in the stools the tongue and mouth appear unaffected and the diastatic reaction of the urine is high In pancreatogenous steatorrhea the nitrogen loss in the stools is much greater than in sprue the trypsin content of the duodenal juice is markedly reduced and there is a normal or diabetic type of glucose tolerance curve

Pellagra

The presence of a glossitis and diarrhea in pellagra may simulate sprue but usually the mouth lesions in pellagra are more extensive and severe The anemia is not so pronounced macrocytes in the peripheral blood are not frequent except when the disease develops in chronic alcoholics but rarely is the bone marrow found megaloblastic The characteristic symmetrical skin lesions and the frequent mental symptoms will establish the diagnosis of pellagra

Celiac Disease

Celiac disease is also known by various names including Gee Herter s syndrome but is known to Thaysen Hanes and other investigators as *infantile sprue* It is a disease of unknown etiology occurring in children under 10 years of age and associated with diarrhea flatulence stunted growth and incomplete sexual development The stools are similar in appearance and in chemical composition to those of sprue The anemia is not so marked and is usually of the hypochromic type Response to liver therapy is not so striking but a high protein low fat and carbohydrate diet is a more important therapeutic measure than liver therapy

Idiopathic Steatorrhea

Gee Thaysen s disease is probably the prolongation of celiac disease into adult life a nutritional disturbance associated with tetany osteomalacia infantilism and megacolon and characterized by a hypochromic anemia and disturbance of the calcium metabolism To some investigators the so-called nontropical sprue is nothing but idiopathic steatorrhea

We do not believe that sprue is a prolongation of celiac disease into adult life Our cases of sprue apparently have not suffered from celiac disease in infancy furthermore we see a great many more cases of sprue in the tropics than the pediatricians see cases of celiac disease

Tropical Macrocytic Anemia

This condition cannot be differentiated from sprue on blood and bone marrow studies though determination of the serum iron which is lower in tropical macrocytic anemia may be of some help The condition occurs more

often in pregnant women living in the tropics and is not accompanied by diarrhea A clear cut history of dietetic inadequacy is usually obtained in the so called tropical macrocytic anemia

Obstruction to the Lacteal Flow of Chyle

Obstruction to the lacteal flow of chyle from the intestines may produce severe steatorrhea which may be confused with sprue Tuberculosis cancer or fibrosis of the mesenteric lymph glands are the most frequent causes of such obstruction These may give rise to a sprue like clinical picture but the laboratory will readily clarify the diagnosis The anemia in these conditions is commonly hypochromic and the bone marrow is not megaloblastic

Rewell (1944) of Guy s Hospital in England reports a case of Hodgkin s *sarcoma of the mesenteric glands with steatorrhea megalocytic anemia and* hyperkeratosis and claims that this particular cause had not been recorded before When Hodgkin s disease tuberculosis or cancer of the mesenteric glands give rise to the so called sprue syndrome *it is not sprue* that we are dealing with There will always be lacking some of the clinical features of sprue and other features characteristic of the real or primary disease will be present so that the patient will not usually respond to the accepted and almost specific treatment of sprue

Simmonds Disease and Anorexia Nervosa

Simmonds disease and anorexia nervosa may resemble sprue only superficially The severe cachexia and anorexia are the only features common to the 3 conditions Some of the symptoms of Simmonds disease such as emaciation premature aging gonadal atrophy amenorrhea loss of libido dental caries and loss of teeth microsplanchnia marked depression of the metabolic rate loss of hair from the axillae pubes and scalp and various abnormal mental reactions are observed in sprue the steatorrhea the macrocytic anemia the flat glucose tolerance curve are not observed in Simmonds disease The apathy in Simmonds disease sometimes seen in sprue is contrasted with the remarkable energy seen in anorexia nervosa

THE SKELETON

Investigators of nontropical sprue emphasize the occurrence of tetany, osteoporosis and osteomalacia among their patients Hansen and Staa (1936) describe and illustrate beautiful cases of severe osteomalacia in sprue In our experience in the Tropics we have not yet seen a single case of sprue complicated by osteomalacia The long bones were normal radiologically in a large series of cases only 5 per cent showing areas of decalcification in the costal cartilages Osteoporosis has been occasionally observed in children suffering from sprue but no more often than that observed by us in a survey of a general hospital population of 310 infants and children (Suarez 1945)

Our patients complain rather frequently of cramps in the legs but signs of typical tetany either spontaneous or induced have not been seen

LABORATORY EXAMINATION

Stools

It has been stated that the stools in acute sprue are usually abundant, frothy, acid, white, and fetid A normal individual excretes about 200 Gm of feces daily, while the sprue patient passes from 400 to 1,200 Gm Normal stools contain no fat that can be demonstrated microscopically Stools of sprue patients contain large amounts of fat, which can be roughly determined by staining a fecal sample with Sudan III and examining under the microscope

The pallor of the sprue stool is not due to lack of bile for this is present in normal amounts Our study of urobilinogen content of the stools in acute sprue has revealed a normal or subnormal 24 hours' elimination, as contrasted with pernicious anemia in which the urobilinogen content has often been found increased

Gastric Analysis

The gastric secretion in sprue shows a hypochlorhydria in nearly 70 per cent of the cases and a histamine resistant achlorhydria in about 30 per cent Hyperchlorhydria is extremely rare In a series of 150 cases reported by us, only 1 case showed hyperchlorhydria and not 1 case in a series of 100 reported by Rodríguez Molina, and in 100 cases recently studied at the University Hospital, only 14 per cent had a free hydrochloric acid above 80 degrees

Gastroscopic Findings

Gastroscopic studies on sprue patients have been carried out in Puerto Rico by Rodríguez Olleros (1938) and by Hernandez Morales (1944) In the full blown sprue, the former found atrophy of the gastric mucosa in 9 of 10 cases The examination proved unsatisfactory in the remaining case Rodríguez Olleros expressed the opinion that the atrophy of the gastric mucosa in pernicious anemia was more intensive than in sprue Of 9 cases with the "incomplete syndrome" he found slight atrophy in only 3 cases In the other 7, there were "alterations of the gastric mucosa without however, any definite characteristics" Of the third group of 9 patients examined—with the "latent sprue syndrome"—a normal mucosa was found in only 3 It is interesting to observe that hypertrophic gastritis was found in 3 of these last patients Rodríguez Olleros expressed the belief that "the atrophic gastritis that accompanies the full blown syndrome of sprue appears during the height of development of the clinical picture and does not precede it "

Hernández-Morales performed 61 gastroscopic examinations on 36 patients suffering from sprue during the acute diarrheal stage and after liver extract had been given for varying periods of time In 55 per cent of the patients atrophic changes were observed in the gastric mucosa Practically all the patients who showed acute glossitis with absence of papillae recovered completely following liver extract therapy Of 16 patients who were re examined with the gastroscope after treatment, 10 (62 per cent) showed a normal gas

tric mucosa Rectosigmoidoscopic examinations also performed by Hernandez Morales during the acute diarrheal stage revealed several types of lesions such as patches of atrophy edema friability purpuric spots and superficial inflammation

Ruffin (cited by Hines 1943) from the Duke Hospital Clinic reported atrophy of the gastric mucosa in 40 per cent of 20 cases studied ' However there is no constant gastroscopic picture in sprue Active cases may present a normal gastric mucosa and occasionally one will see atrophy in patients who have recovered

It is evident from these studies that the gastric mucosa in sprue as well as in pernicious anemia is frequently atrophic but that it probably has a greater tendency to become normal This may be explained by the fact that sprue patients are usually younger and therefore recover more easily and more rapidly than patients with pernicious anemia who are generally older persons

Roentgen Studies of the Intestinal Tract

According to May and McCleary (1941) clumping in roentgenograms of the small intestine of infants and children with the celiac syndrome was noted by Blackfan and Vogt as early as 1930 Zwerling and Nelson (1943) found in a study of 77 presumably healthy infants and children wide variations in the intestinal pattern and believe that the roentgenologic appearance of the small intestine is not at the present time a reliable criterion for the diagnosis of nutritional deficiency states in infants and children They thought that emotional disturbances are among the factors that must be considered to explain the observed intestinal patterns

The interest in the roentgenologic investigation of the gastrointestinal tract in sprue was aroused by the observations of Mackie (1933) and by those of Snell and Camp (1934) who found that the characteristic picture after a barium meal is that of delayed motility and alteration of the mucosal relief of the small intestine especially the jejunum the contour of the bowel is smoothed out the usual markings of the valvulae conniventes are obliterated and the barium is clumped in elongated masses

The changes observed have been grouped under the term deficiency pattern and include hypermotility and hypomotility hypertonicity hypotonicity dilatation of loops segmentation coarsening and obliteration of the mucosal folds and flocculation of barium

Subsequent studies and observations by Miller and Barker (1937) Mackie and Pound (1935) Kantor (1939) Miller and Rhoads (1936) and Lepore and Golden (1941) not only of sprue but of various other conditions have tended to establish the deficiency pattern or the so called moulage sign or clumping of the barium meal as roentgenologic evidence of deficiency state present in the steatorrheas and in deficiency of the B complex without steatorrhea Krause and Crilly (1943) added infestation with *Necator americanus* to the list of the following conditions which have been found to produce deficiency pattern of the small intestine celiac disease tropical and

nontropical sprue pellagra peptic ulcer cancer tuberculosis of the small intestine biliary and pancreatic disease chronic ulcerative colitis regional ileitis sclerosing inflammation of the mesenteric lymphatics hypoproteinemia diabetes insipidus parathyroid disease and allergic states Hernandez Morales and Ruiz Cestero (1945) have recently added *Schistosoma mansoni* In a study of 47 cases they reported the characteristic x ray pattern of deficiency disease in 31 9 per cent

Golden (1941) did not find the deficiency pattern in 15 cases of pernicious anemia

Hurst s theory (1942) in explanation of the defective absorption of fat by the sprue patient based on x ray evidence of impaired motility of the small intestine lost its weight when Golden showed that similar defects were seen



Fig 444 —Typical moulage sign in sprue

in various other conditions unaccompanied by steatorrhea Hurst suggested that the muscularis mucosae is paralyzed to a greater or less degree and that paralysis of the extension of the muscularis mucosae into the villi would result in cessation of the pumping action of the villi necessary to intestinal absorption This functional failure of the muscularis mucosae might be due according to Hurst to absence of the unknown constituent of the chyme which is the chemical stimulant of Meissner s plexus or to the effect of vitamin deficiency or to some specific or nonspecific toxemia on the plexus or less probably on the muscularis mucosae

May and McCreary (1940) in a study of 40 instances of celiac disease demonstrated that the dramatic effects of mecholyl (acetyl β methylcholine) on the behavior of the intestine in these persons were interesting and sig

nificant' Within a few minutes after the administration of the drug the picture of clumping of the barium meal into inactive masses in the dilated bowel was completely transformed by the action of the mecholyl A vigorous segmental and peristaltic activity commenced within 1 to 3 minutes after the drug was given The tone returned to the bowel and the lumen became normal in size The small intestine appeared normal throughout and even the feathery character of the jejunum returned Along with this improvement in motility an increased rise in the blood sugar curve occurred In fact a normal rise in the blood sugar was obtained in every patient in whom this experiment could be attempted Flax Barnes and Reichert (1942) showed that the administration of Prostigmine can change the "deficiency pattern" as seen in fibrocystic disease of the pancreas and improve the absorption of the fat soluble vitamin A

With Ruiz Costero of our Department of Roentgenology, we have studied the gastrointestinal tracts of 71 cases of sprue In 70 per cent clear cut radiologic evidence of "deficiency pattern' was observed The normal feathery or delicate herringbone appearance of the valvulae conniventes with an even contour and normal size of the intestinal lumen was obtained in 30 per cent of the cases The stomach was found normal in 80 per cent of the cases 20 per cent showing signs of gastritis This study confirms the already established idea that in sprue most of the roentgenologic evidence of disease is found in the small intestine especially the jejunum

Blood Chemistry

Studies in blood chemistry were performed in 100 cases with the following results

Glucose was found to range between 70 mg per 100 c c of blood and 150 mg per 100 with an average of 94 8 mg per 100

Urea nitrogen ranged between 8 and 20 mg per 100 c c with an average of 9 8 mg

Nonprotein nitrogen ranged from 15 to 76 2 mg per 100 c c with an average of 25 8 mg

Total plasma proteins ranged from 4 5 to 9 5 Gm per 100 c c with an average of 7 2 Gm

Serum albumin ranged from 1 5 to 6 Gm per 100 c c with an average of 3 8 Gm

Serum globulin ranged from 1 5 to 5 Gm per 100 c c with an average of 3 1 Gm

Calcium serum ranged from 6 to 11 mg per 100 c c with an average of 8 1 mg

Phosphorus inorganic serum ranged from 1 5 to 5 mg per 100 c c with an average of 3 3 mg

Phosphatase ranged from 1 to 11 1 Bodansky units with an average of 3 5 units

Cholesterol, blood, ranged from 60 mg to 190 mg per 100 c c, with an average of 127 mg per 100

The values for *uric acid, creatinine,* and *chlorides* were normal The *icterus index* was usually found below 6 In our series of 150 cases of sprue reported in 1938, readings over 10 units were obtained in 15 cases and readings of 20 units in 3 cases

The Blood

The anemia of sprue is so exactly similar to that of pernicious anemia that, for all clinical purposes, it may be considered identical We doubt that even the most expert hematologist can differentiate the 2 conditions from the study of the peripheral blood or bone marrow The anemia of sprue is most constantly of the macrocytic type, usually hyperchromic occasionally hypochromic, very rarely normocytic but never microcytic (Suarez 1931, 1932)

Several textbooks and manuals of tropical medicine state that in the early stages of the disease there is commonly a moderate microcytic anemia We must confess that we do not see those early cases in this part of the world and that in our experience a diagnosis of acute sprue in the presence of a hypochromic microcytic anemia rarely proves correct

With the exception of one case (a patient whose marrow was probably in a hypoplastic state), in which the mean cell volume was 89 cubic microns the lowest mean cell volume was 102 cubic microns, the highest 220, and the average 123 6 cubic microns

The color index was found below 1 0 in 23 cases, and 2 cases were as low as 0 70 and 0 64, respectively The highest color index was 2 2 and the average 1 22 The volume index was never found below 1, the highest was 2 3 and the average 1 39

The mean cell hemoglobin varied between 26 and 59 micrograms, with an average of 36 6 micrograms

The mean cell hemoglobin concentration was found at 22 per cent, or lower, in 4 cases, the lowest figure being 20 per cent The highest was 45 per cent, with an average of 26 1 per cent

The hemoglobin ranged from 16 5 to 102 per cent, averaging 66 per cent, the erythrocytes from 690,000 per cubic millimeter to 4,410,000 per cubic millimeter, with an average of 2,710 000 There was usually leucopenia with relative lymphocytosis The lowest leucocytic count was 1,550 per cubic millimeter, the highest 13 600, and the average was 5 280 leucocytes per cubic millimeter

The presence of hypersegmented neutrophiles in increased number has been described in pernicious anemia as well as in sprue

The Sternal Marrow

The bone marrow obtained by aspiration of the sternal marrow usually shows a hyperplastic picture with an increase in megaloblasts, indistinguishable from pernicious anemia A previous administration of a potent liver

Fig 445



Fig 446





Fig 447



Fig 448

Fig 445.—Megaloblasts in sternal marrow of sprue
Fig 446.—Sternal marrow in sprue Erythroblastic arrest.
Fig 447.—Sternal marrow in sprue after folic acid Maturation effect
Fig 448.—Sternal marrow in sprue after folic acid Normoblastic response

preparation or of folic acid is likely to modify in as short a time as 24 hours the typical bone marrow picture of sprue The effect may persist for weeks and even months

A rapid maturation of the megaloblasts in the bone marrow takes place following the administration of liver extract or of folic acid

Hemodynamics

In contrast to the compensatory hypertrophy of the heart observed in the iron deficiency anemia associated with hookworm disease (Porter 1937) the heart of sprue patients is usually found to be small (all viscera are) both radiologically and postmortem

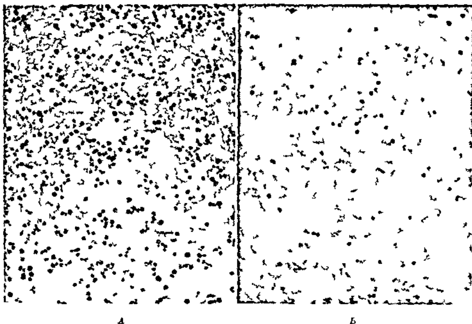


Fig 449—Sternal marrow aspiration of sprue patient A On entry B one month after beginning of folic acid treatment

Hashimoto (1937) quotes Alsmeer and Wenckebach by stating that there exists a group of heart muscle disturbances in deficiency diseases such as beriberi and rickets that have some characteristics common to all of them He describes a case of pernicious beriberi with cardiac dilatation and hypertrophy successfully treated by intravenous administration of vitamin B Weiss and Wilkins (1937) of Boston have dealt with the subject of beriberi heart

The probably *inadequate content of vitamin B complex in the Puerto* Rican diet and the fact that some cases of sprue have been benefited by the administration of vitamin B concentrate marmite or autolyzed yeast made us focus our attention on the heart However because sprue patients are usu

ally ambulatory, except during the most severe episodes of diarrhea, we logically expected a compensatory mechanism in the cardiovascular system

If there is a compensatory mechanism in the cardiovascular apparatus of sprue patients it is certainly not based on hypertrophy of the cardiac muscle The concomitant infestation with *Necator americanus* (56 per cent) and *Schistosoma mansoni* (20 per cent) did not modify the tendency to small or normal cardiothoracic ratios

The blood pressure is low, both systolic and diastolic, and goes *pari passu* with the state of emaciation and asthenia shown by the patient We do not know as yet whether the hypotension is an expression of the generalized bodily weakness or whether it is due to a diminished output of pressor substance by the adrenals The fact is that following adequate treatment and apparent recovery, the blood pressure becomes normal in the younger patients, and in the older ones, as reported by us in 1938, there is a tendency for hypertension to develop

The *vital capacity* of 18 of the 25 cases studied was found to be anywhere from 200 to 1,200 c c below the estimated capacity for the specific individuals, in 3 cases, the actual and predicted capacities were equal, and in only 4 was the former higher than the latter In another series of 35 cases recently studied, the vital capacity ranged from 750 c c to 5 000 c c, the average being 2,292 c c It should be stated that the height and size, and consequently the surface area, of the average Puerto Rican is less than that of the continental (U S) individual

The *cardiothoracic ratio* averaged 44 per cent, of the 25 patients, only 1 had a cardiothoracic ratio of over 50 per cent, 4 had one of 42 per cent, 1 each of 40 and 41 per cent, and 2 of 39 per cent Of 65 cases studied at the University Hospital, 47 (80 per cent) showed a Danzer ratio of less than 1, and 18 or 20 per cent, of over 1

The *electrocardiographic studies* were essentially negative Findings suggestive of beriberi heart were never encountered, and evidence of myocardial disease was rarely observed

The *circulation time* was also found within normal limits, 12 seconds being the average for the arm to tongue measurements using either sodium cyanide, calcium gluconate, or fluorescein

The *venous pressure* ranged within normal limits in the majority of cases The range was from 40 to 140 mm of water, the average 90 mm

The *blood volume*, as determined with the Congo red method in 38 cases of acute sprue, also ranged from 1 000 to 6,000 c c, with an average of 3 400 c c, the plasma volume from 1,000 to 5,000 c c, with an average of 2 590 c c The blood volume per kilogram of body weight ranged from 60 to 110 c c, with an average of 79 c c

Carbohydrate Metabolism

Except for 3 instances the fasting blood sugar was found to be low in 40 cases studied by us in 1938 In a new series of 70 cases studied at the University Hospital, the fasting blood glucose ranged between 70 and 180

mg per cent, with an average of 94 8 mg per 100 c c of blood Hypoglycemia of 70 mg per cent, or less, was observed in only 3 cases

The occurrence of a flat glucose tolerance curve, reported by Thaysen (1932) and by Hanes (1935) in nontropical sprue and by Fairley in tropical sprue, has been corroborated by us When the sprue patient ingests 1 Gm of glucose per kilogram of body weight the increase in blood sugar rarely goes above 40 mg per 100 c c

In our original 40 cases (1938) only 4 patients showed an increase of over 40 mg per cent in their blood sugar after the oral administration of glucose Unpublished data on 100 new cases showed approximately 80 per cent with elevations of less than 40 mg per cent in their blood sugar The discrepancies in the results obtained in these 2 series may be explained by the fact that liver extract had been administered more often to patients of the new series before admission to the hospital than to those of the previous group As it has been observed in other conditions and in about 5 per cent of normal individuals the flat or low blood sugar curve is not pathognomonic of sprue, but it certainly has diagnostic and prognostic value

According to Thaysen the sugar curve tends to return to a normal level as the patient recovers In our experience this is true in most of the younger patients whose gastrointestinal canals have not yet suffered irreversible changes After complete restoration to normality of the clinical and hematologic picture and while still under parenteral liver therapy older patients often give a flat glucose tolerance curve As already observed by Hanes and McBryde (1936) blood sugar curves are high when glucose is administered intravenously This fact together with the observations of Barker and Rhoads (1937) favors the theory of a deficient intestinal absorption and tends to make the hypothesis of pancreatic disease less important in our understanding of sprue

Furthermore, Hanes and Reiser (1940) concluded from their studies of the relation of phosphorus to glucose metabolism in sprue and from respiratory quotient determinations after oral and intravenous glucose tolerance tests that their findings reflect a slow rate of intestinal absorption by the sprue patient

Protein Metabolism

The fact that trypsin and erepsin are not lacking in sprue explains the finding that proteins are well digested and absorbed

The severe diarrhea of sprue may cause a moderate loss of nitrogen in the feces, but with a fairly high intake of animal protein the patient is able to store nitrogen

Basal Metabolism

Thaysen declared that celiac disease nontropical sprue, and tropical sprue are one disease He sets the following clinical features as characteristic (1) abnormal excretion of fat in the feces, (2) normal, and in rare cases slightly raised nitrogen excretion in the feces, (3) flat blood sugar curve and (4) increased basal metabolism He stated, furthermore, that the com

bination of these 4 manifestations of altered metabolism does not occur in any other but the 3 diseases mentioned above

At the Duke Hospital Clinic they have noted the greatest irregularity in the basal metabolic rates in sprue the test lacking all usefulness in differential diagnosis They believe that the findings in sprue are similar to those recorded in the anemias and are not related to the thyroid

Our experience agrees with that of the group at Duke The readings in a small number of patients ranged from +4 to −23 per cent, but there was a tendency toward a low basal metabolic rate as might be expected because of the state of asthenia and inanition of the patients

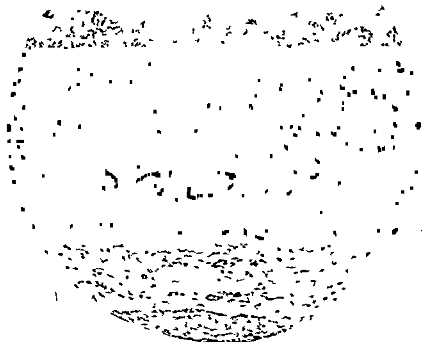


Fig 450—Pyloric portion of the stomach in a case of sprue Despite the autolysis the paucity of glands their slight cystic dilatation the colonic conversion of glands and the round cell infiltration are clearly visible ×80 (Courtesy of F Koppisch)

PATHOLOGIC ANATOMY

In a total of 1,356 autopsies performed from 1926 to 1943 at the School of Tropical Medicine, 16 cases of sprue were found In a review of these 16 autopsies the following were the principal findings (Koppisch*) The body

*Personal communication Koppisch F Department of Pathology School of Tropical Medicine San Juan Puerto Rico

was markedly wasted and the viscera were atrophied particularly the heart spleen and liver The fatty tissue in all areas had undergone serous atrophy The walls of the stomach and small intestine were thinner than normal in ½ the cases, that of the colon in ⅓ The lingual mucosa was smooth with atrophied papillae in about ⅓ All organs and tissues were very pale from the anemia The bone marrow in the middle third of the femur was of variable appearance (1) red and diffusely hyperplastic (2) pale and of gelatinous aspect but with red foci of activity and (3) diffusely pale semitranslucent



Fig 4a1 —Section of ileum in sprue showing broadening of villi and dense infiltration of propria with plasma cells and lymphocytes Formalin was injected into the abdominal cavity immediately after death ×80 (Courtesy of [illegible])

and gelatinous Microscopically the 3 types corresponded respectively to diffuse hyperplasia of megaloblastic type to foci of hyperplasia of the above type in an otherwise inactive marrow showing serous atrophy and to complete hematopoietic inactivity and far advanced serous atrophy of the medullary fat

Other microscopic findings of interest were brown atrophy of the myo cardium atrophy of Malpighian corpuscles in the spleen atrophy hemo

siderosis, and edema of the liver, advanced depletion of lipoids in the suprarenal cortex, accompanied by cortical atrophy and occasional focal loss of tissue in the fasciculate zone, which became replaced by lax scars, and a marked reduction of spermatogenesis in the male Atrophy of pancreatic acini was seen in ⅓, and a very slight interstitial fibrosis in 2 of 15 cases Findings in the gastrointestinal tract consisted of round cell infiltration and hypervascularization of the subepithelial connective tissue of the tongue in all



Fig 452—Broadened villus in a case of sprue with dense infiltration of propria with round cells X360 (Courtesy of E Koppisch)

cases The lingual mucosa showed atrophy in ½ of them and zones of atrophy, alternating with hyperplasia, in the remainder The gastric mucosa was moderately atrophied in ½ the cases, while there was chronic gastritis in all but 3 A distinct shortening and blunting of the villi of the small intestine was noted in ½ the cases, accompanied by an increase in the number of plasma cells in the tunica propria The remaining cases presented no detectable abnormalities, except for occasional edema of the submucosa The colon was normal in only 3 cases An acute colitis, in most instances mild, was found

in 7, and a few nonspecific ulcers in 6 In 3 the mucosa seemed thinner than normal while in 4 there was atrophy of the muscle coats The spinal cord was examined in only 5 cases a combined degeneration not having been found in any

The internal organs were small The weight of the liver varied from 720 to 1 020 Gm with an average of 1 066 Gm (normal 1 400 to 1 600 Gm) the heart weighed from 140 to 270 Gm with an average of 230 Gm (normal 280 to 300 Gm) and the spleen weighed from [illegible] to 140 Gm with an average of 74 9 Gm (normal 125 to 150 Gm)

TREATMENT

We had said (1938) that unquestionably the 2 most important factors in the treatment of sprue are an appropriate diet and an adequate liver therapy Today we can modify that statement thus an appropriate diet and adequate liver therapy or sufficient folic acid

Such drugs as hydrochloric acid calcium vitamin D phosphorus pancreatin cholagogues and glandular extracts are valueless in the treatment of tropical sprue Iron in large doses is sometimes necessary during the course of treatment Its use during the active stage of the disease is not only ineffective but may be deleterious It is our opinion that a diet rich in proteins and low in fats and carbohydrates as insistently recommended by Ashford is essential for the well being of the patient at least while he resides in the tropics

Miller and Rhoads (1935) said that unless a sufficiently large amount of liver extract was administered at frequent intervals flatulence intestinal discomfort cramps and diarrhea recurred in sprue patients that this was the case despite the fact that no detectable hematologic disturbance was present Thus intestinal dysfunction they say rather than the anemia has been the guide for the administration of therapy

Subsequently Miller and Barker 1937 modified the above statement saying The maintenance of a diet for sprue in addition to liver therapy gives a patient more complete relief from gastrointestinal symptoms than does liver extract alone

Manson Bahr claims to have obtained good results in the treatment of sprue with nicotinic acid (30 mg daily for 1 month) if angular cheilitis is present by the addition of riboflavin (3 mg daily) The glossitis heals within 4 days and the intestinal symptoms especially the meteorism improve shortly afterward Finally the diarrhea ceases entirely and the stools become normal Indeed it seems he says to be the most satisfactory method of treatment for tropical sprue yet introduced He does not claim however that vitamin B_2 treatment has any beneficial effect upon the anemia which should be treated at the same time with intensive parenteral liver therapy

We have reported (Suarez 1935 1931) the therapeutic failure in sprue of certain preparations considered potent in the treatment of Addisonian pernicious anemia Ventriculin Extralin and autolyzed liver extract have failed

in sprue The failure cannot be attributed entirely to deficient gastro-in testinal absorption for in many cases we have found aqueous liver extrac (Valentine) inducing rapid clinical and hematologic improvement We hav reported the highest reticulocyte count observed in sprue (65 per cent) in patient who received aqueous liver extract per os after full doses of Ver triculin administered during 15 days had had no effect It is generally ad mitted that sprue patients respond more readily to the parenteral administr tion of liver extract than to its oral ingestion

We have had experience with most of the American and some of th European liver extract preparations especially with Lilly's 343 which h been found efficient in the treatment of sprue The parenteral administratio of this preparation in doses of 6 c c daily to 35 cases of sprue gave a reticul cytic response of 1 5 per cent (the lowest) and of 42 per cent (the highest in a patient whose initial red blood cell count was 990 000 per cubic millimete The average reticulocytic response was 10 5 per cent

Lilly's 343 is a relatively crude or diluted extract high in ash togeth with a large percentage of inert material It undoubtedly carries an apprec able amount of what we may call the B complex and is highly beneficial in th treatment of sprue anemia

Contrary to expectations concentrated liver extract (Lederle) containin not more than traces of the various vitamin B components (200 800 gamma o folic acid per cubic centimeter) also proved effective in sprue Rapid clinic and hematologic improvement followed its parenteral use in 1 c c daily dos for 3 consecutive days then 1 c c every third day for the first month and c c every 5 days during the second month The maintenance dose was 1 c every 5 to 7 days The lowest reticulocyte response in 70 cases was 2 per cen in the group of patients having an initial red blood cell count of ove 3 500 000 the highest count was 35 5 per cent in a case with an original coun of only 830 000 erythrocytes The average reticulocytic response was 10 per cent exactly the same figure obtained with Lilly's 343

Using diluted extracts we obtained a higher reticulocyte response in th group of patients with less than a million red blood cell count In all othe groups with 1 5 million and over the reticulocytic rise induced by the con centrated liver extract compared favorably not only with that produced b other crude extracts but also with the standards subscribed by the America Medical Association for the potency of liver preparations on perniciou anemia

The sprue case as a rule improves dramatically for the first 10 days t 1 month or 1½ months under appropriate diet and parenteral liver therap However in spite of large doses of liver and the addition of iron the progre from then on is very slow and tedious so much so that only few cases reac an absolutely normal blood picture at the end of 2 months Fifty two pe cent had at the end of that period a predominance of macrocytes as evidence by a persistent mean cell volume of over 100 cubic microns

In our series of 150 cases 2 presented allergic reactions during the intra muscular liver therapy, in both cases the medication had to be given up On

developed asthma rhinitis urticaria and migraine all at the same time, and the other showed a very marked angioneurotic edema

In the above mentioned series there was only 1 death which occurred shortly after admission before a complete blood study could be made The diagnosis was made at autopsy *

Diet

We believe that an appropriate diet high in good proteins low in fats and carbohydrates is an important adjuvant in the efficient treatment of sprue

Before the advent of liver therapy (Bloomfield and Wyckoff 1927) Chinese physicians used marmite soup and Sir Patrick Manson recommended liver soup (1883) in the treatment of sprue

Several different diets have been advocated from time to time the fruit or strawberry diet of van den Bergh the milk diet of Manson and the raw meat diet of Cantlie Each one of these investigators believed that sprue patients should eat nothing but their respective diets for several weeks if improvement was to be expected Undoubtedly many cases of sprue responded favorably to these diets Fairley (1930) successfully employed a series of graded high proteins low fats and low carbohydrate diets with an energy value varying from 700 to 3 000 calories and having a protein fat carbohydrate ratio of 1 0 0 3 1 3 instead of the usual 1 0 1 0 4 00 ratio The source of protein was lean meat Later (1932) Fairley recommended *Prulac* a defatted high protein milk powder As the intestinal symptoms subside and the stools become soft or formed diets of increasing caloric value are gradually substituted, a convalescent high protein diet including fruits and vegetables being generally allowed about the fifth or seventh week

Eggnog milk or fresh fruits may be eaten between meals Meat should be lean and rare beef lean roast or steak lamb lean roast or chops ham lean liver tongue heart kidney or sweetbreads fish any fresh fish lobster crabs or oysters Milk and milk products milk buttermilk and American and cottage cheese usually agree with the patient Eggs may be prepared in any desired manner

All fatty foods should be avoided butter cream lard olive oil and oil salad dressing avocado pears pie pastry and food fried in fat All starchy foods should be avoided potatoes corn bread cereals cake candy

The following are copies of the menus for sprue patients used at the University Hospital of San Juan Puerto Rico

Full Sprue Diet

BREAKFAST

Fruit juice (containing vitamin C)—1 full glass (8 oz)
Cereal—Whole grain as oatmeal Wheaties or enriched cereal
Eggs—at least one soft boiled or poached (egg can be given in some other meal if desired)
Coffee with milk

* Editor's note (O F) Since this chapter was prepared for print vitamin B_{12} has proved to be an effective adjuvant in the treatment of sprue

10 00 A M

Fruit juice, banana, milk (one or all)

LUNCH

Soup (large serving)—Meat stock, not much fat, served with a piece of meat and several vegetables cut in small pieces and cooked in the meat stock, tomatoes and green vegetables to be used as often as possible

Viands—*Served on the side if desired*

Bread—Served with oleomargarine or butter

Dessert—Bananas should be served frequently, not too many starchy desserts

Milk—One glass

3 00 P M

Fruit juice, banana, milk (one or all)

DINNER

Meat—All forms, except fried, not too much pork

Salad—Large serving, including lettuce and at least one other raw vegetable, with other low carbohydrate fruits and vegetables

Bread—Served with oleomargarine or butter

Dessert (See directions for lunch)

Milk—One glass

Diet should supply each day at least 1/4 pound of meat, 3/4 quart of milk, 1 egg 4 bananas (more are better), some raw vegetables or fruits other than bananas, 1 teaspoon*ful salt (approximately 7 grams)*

Noodles macaroni and spaghetti should not be used Rice and beans may be served once or twice a week Crackers should be served sparingly if at all Second servings *should be available for those desiring more food*

Blood Transfusions

Small and repeated blood transfusions are lifesaving measures which should not be neglected in the treatment of the very ill, profoundly anemic, and cachectic patient

Folic Acid Treatment

Folic acid known for some time as one of the components of vitamin B complex, is at present considered identical to the *Lactobacillus casei* factor recently synthesized by 16 investigators of the Lederle Laboratories and the *Calco Division of the American Cyanamid Co (Angier et al, 1945)* As it was isolated from green leaves including grass Mitchell, Snell, and Williams (1941) named the substance "folic acid," from "folium" the Latin name for leaf Folic acid is present in descending concentration in the adrenals liver, kidney, and colon It is also found in yeast and in mushrooms

Spies and his group (1945) (Vilter et al, 1945) of the University of Cincinnati and the Hillman Hospital at Birmingham Alabama were the first to report on the antianemic properties of synthetic folic acid on the macrocytic anemias Thirteen of the 14 patients treated showed positive *hematologic response* The material was given intravenously, intramuscularly, and orally Erythrogenesis occurred regardless of the route of administration of folic acid and regardless of the clinical classification as to pernicious anemia or nutritional macrocytic anemia



Fig 4?3—Case ? 9? Sprue A On admission showing severe cachexia, somewhat distended abdomen with doughy feeling on palpation *B* same patient weighing 58 pounds some edema of legs and face *C* same patient after 2 months of treatment with folic acid weight 10? pounds



Fig 454—Reticulocyte response to folic acid on seventh day in a case of sprue

Fig 455—Case 10 A 7939 Sprue Reticulocyte hemoglobin and erythrocyte response to therapy

The group of investigators from the Vanderbilt University School of Medicine at Nashville Tenn including Darby Jones and Johnston (1945 1946) reported on the use of synthetic *L casei* factor in the treatment of sprue They administered 15 mg of folic acid intramuscularly daily with good hemato poietic response in 2 cases

Again it was Spies and his collaborators (1946) of Cuba and Cincinnati who first used folic acid in tropical sprue They reported their preliminary observations on 3 cases treated in Havana in November 1945 Spies has a working hypothesis to explain the action of folic acid He believes that folic

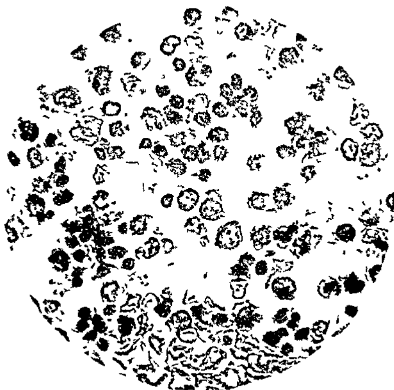


Fig 456 —Sprue Normoblastic response observed in the aspirated sternal marrow following adequate therapy

acid in food occurs as a conjugate and that in view of Castle s work it is likely that in pernicious anemia the enzymes are unable to liberate efficiently the folic acid whereas in sprue pellagra pregnancy and nutritional macrocytic anemia the folic acid or substances that act similarly are made more available They proved that folic acid has a striking antianemic effect in 5 types of macrocytic anemia Addisonian pernicious anemia nutritional macrocytic anemia macro cytic anemia of sprue macrocytic anemia of pellagra and macrocytic anemia of

pregnancy There is not yet a satisfactory explanation concerning the fact that a fairly large amount of folic acid is required to produce a maximum hematopoietic response in contrast to highly potent liver extract in which the active substance is apparently smaller

On Dec 1, 1945, in collaboration with Dr Spies, who brought with him from Cuba the first supply of the drug, we began to use folic acid in sprue At present we have treated 21 new cases of sprue and have shifted to folic acid 29 old cases who had been under parenteral liver therapy for a number of months or years The results obtained so far have been very promising

In the presence of an adequate sprue diet high in animal proteins and low in fats and carbohydrates, the oral administration of 10 mg of folic acid daily is adequate even in the presence of severe diarrhea

PROGNOSIS

The prognosis is good for old and recent cases provided they receive adequate treatment and appropriate diet Instances of sprue refractory to intensive therapy are extremely rare The mortality at present is low The death rate from sprue in Puerto Rico during the last few years has remained stationary at approximately 59 per million inhabitants

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CHAPIER 61

BERIBERI

EUGENE R WHITMORE

DEFINITION

The name beriberi comes from a Singhalese word meaning weak ness or cannot in the sen e that the patient is too ill to work the duplication of the term indicates the outstanding importance of this feature of the condition The synonym kakke in China and Japan means a disease of the legs thus again indicating the importance of this feature of the disease

Today the condition is known to be a deficiency disease due funda mentally to a deficiency of vitamin B (thiamine) * and characterized by muscular weakness peripheral neuritis edema or wasting and cardiac failure

ETIOLOGY

The story of the development of ou knowledge of the et ology of ber beri is the story of one of the outstan l ng developments n med cal knowledge The d sease s ment oned by Strabo and P o Cass us as a d sease which attacked a Roman army n Arab a n 24 B C and kakke is ment oned n a Cl nese pamphlet of the second century B C and s m nutely descr bed n a pamphlet of the seventh century it is recorded as occurr ng n Japan in the n nth century In the tenth century a d stinct on was made between the atroph c dry or paralyt c form and the hypertroph c wet or drops cal form In 1758 Bont us as the first European doctor to g ve a descr pt on of the disease wh ch he called ber ber From that t me on reports ere made from d fferent parts of the world giving r se to the cons derab e number of synonyms for the disease n various countr es including h nchazón (s ell ng) in Cuba and inchaçao (swell ng) and perne ras (disease of the legs) n Braz l

During Wo ld War I there was a ber ber l ke d sease among European troops in Mesopotam a and the Dardan lles ber beri was not uncommon among our men who were pr oners of the Japane e du ng Wo ld War II an l those men are fam l ar with the term ber be heart

One obta ns eloquent test mony to the mportance of the d sease when he reads the l st of causes that were suggested and stud ed all the way from atmospheric con d t ons through chem cal causes bacter al po sons and infect ons to food defc enc es

As the endem c area of ber ber as in tl e Or ent Fas ern As a Japan tl e Ph l pp ne I lands Indo Ch na Java and Malaya—where a pr nc pal art cle of d et was r ce t was natural that r ce should have come under usp c on r ce w thout husk stale or badly kept r ce the tox n of some orga sm l ng n the r ce espec ally n the husk

But the d sea e occurred n Braz l the Moluccas and L ugga where the d et is sago fish and game and where r ce wa not eaten al o n Labrador and Newfoundland where wh te wheat flour is a very mportant part of the d et

The lea that the d sea e as n soc ated w t bu ld ngs ha t ga ned credence and n th s connect on one must refer to the exper mental study carried out at Kwala Lum

*Th s places ber beri n the group of nutr t onal d ficiency d seases and so extends its range far b yon l the trop s

pur, in 1895 The mortality from beriberi in the new jail was high, so a number of prisoners with beriberi, as well as some healthy prisoners were transferred from the new jail to the old jail, all prisoners at both jails being fed rice that was all cooked together at the new jail, so the prisoners in both jails received the same diet it was shown that the building had nothing to do with the occurrence of beriberi One of the outstanding recollections of the author is his visit to Fraser and Stanton at Kwala Lumpur

There had now developed the idea that the disease was due to some deficiency in the diet—protein or nitrogen deficiency It was also recognized that beriberi was often associated with other conditions, which led to some confusion regarding the nature of the disease, and it was placed in a group with polyneuritis of birds Eijkman (1890) observed polyneuritis in chickens fed on polished rice and considered the condition the same as beriberi in man Frazer and Stanton showed that healthy coolies developed beriberi when fed on white rice, while others fed on brown rice remained healthy, and they cured beriberi in man, and polyneuritis in fowls, by adding rice polishings or an extract of them to the diet

Prior to 1884 ⅓ of the sailors in the Japanese navy were disabled by beriberi Takagi, in 1885, replaced part of the polished rice by meat, beans, milk, wheat, and barley and vegetables and the incidence of the disease was decreased enormously Braddon noted that, in the Malay States, the Tamils ate unpolished rice and did not develop beriberi, while the Chinese who ate polished rice developed beriberi

In 1901 and 1902, an outbreak of beriberi occurred in Bilibid Prison in Manila—associated with an outbreak of scurvy, both diseases disappeared when a diet rich in vegetables was given

But there was still the idea of some microbic etiology—perhaps more especially among those of us who had paid special attention to the bacterial and parasitic causes of disease

In 1912, Funk gave the name "beriberi vitamin" to a substance contained in the subpericarpal layers of the rice grain, which was readily separable, and which he considered to be essential for the metabolism of the nervous tissue, and through deficiency of this substance the nervous tissue begins to break down and the symptoms of beriberi appear From that time on, evidence rapidly accumulated that beriberi was a deficiency disease, due to the lack of this "beriberi vitamin" of Funk, later called vitamin B_1, or thiamine because it contains sulfur

This now gave the explanation of the outbreaks of beriberi among people who did not eat rice, such as those who used white bread to excess in the diet Excess carbohydrate in the diet is a factor, as thiamine aids in the oxidation of carbohydrate, fat reduces the requirement Vitamin B_1 is not stored in the body, so deficiency is quickly felt Also, when alcohol furnishes much of the caloric intake, vitamin B_1 deficiency is quickly felt

Since dietary deficiencies are not apt to be single and simple 2 or more of the deficiency diseases are frequently seen in the same patient, thus, beriberi and pellagra are frequently combined, or beriberi and scurvy, as in the Bilibid Prison outbreak

PATHOLOGY AND PATHOLOGIC PHYSIOLOGY

It will be noted that the 2 classical types of beriberi, wet beriberi and dry beriberi, were distinguished in the tenth century, and for a long time there was opinion that the 2 types represented differences which were explained in different ways, indeed, these 2 types were used to argue that there was more than one fundamental cause for beriberi or that the "beriberi vitamin" was not a single substance which was so amply demonstrated later, though on an entirely different basis, and without reference to the 2 types of beriberi Not

so long ago we find it stated that dry beriberi is simply a later stage of wet beriberi (Castellani and Chalmers 1913)

Today, we know that the edema in wet beriberi is due to 2 factors (1) the cardiac failure—cardiac edema and (2) the protein deficiency hypo proteinemia—nutritional edema

Cardiac Pathology

The cardiac pathology consists of increased weight of the heart with thickening of the wall of the right ventricle and with weakness of the heart action This has commonly been described as hypertrophy especially of the wall of the right ventricle though the rapidity with which the heart returns to normal size and function under proper treatment would be sufficient evidence that there is no hypertrophy of the heart The enlarged muscle fibers are vacuolated—hydropic degeneration—the same condition as Scheube described for the heart muscle fibers in rabbits on section of the vagus nerves There is dilatation of the right heart especially of the right auricle which may be greatly enlarged and the wall paper thin

Pathology of the Nervous System

The pathology of the nervous system is important and fundamental the degenerative changes being marked in the spinal cord and in the peripheral nerves Early and marked changes occur in the sciatic nerves and their branches *associated with early involvement of the legs the degeneration* appears first in the myelin sheath with much less damage to the axis cylinders The aphonia is associated with degeneration of the recurrent laryngeal nerves Degeneration of sensory nerves accounts for the paresthesias and anesthesias The *muscles supplied by these nerves are atrophied and give the reaction of* degeneration The degeneration may extend to and involve the sympathetic system

There are no characteristic blood changes Any changes in the blood picture are likely to be due to some associated condition as malnutrition or hookworm disease

SYMPTOMATOLOGY

It is usual to discuss the symptomatology under different forms though the forms may be mixed or one may pass over into the other The course may be acute subacute or chronic

The Rudimentary Form

The rudimentary form is relatively mild the onset is insidious with malaise lassitude loss of appetite dull pain in the abdomen tenderness on pressure over the upper part of the abdomen more or less difficulty in breathing and palpitation of the heart There is a feeling of heaviness and tenderness on pressure in the muscles of the calves of the legs and the muscles are weak less marked in the arms There is frequently slight edema about the ankles and over the shins Soon the patient has difficulty in walking the knee

jerk is at first exaggerated and then disappears and paresthesias develop the patient develops a peculiar step page gait The heart shows enlargement to both sides and murmurs may develop, the systolic pressure is generally normal, the diastolic is low, the pulse is of the water hammer type, but softer than in organic disease of the aortic valve

While the involvement of the legs is usually earliest and most marked, involvement of the nerves and muscles of the arms often develops, and the involvement of the muscles may even extend to the muscles of the trunk

The symptoms may remain slight, or may disappear as a result of improvement in diet, but commonly symptoms associated with one or more of the fundamental pathologic conditions develop and dominate the picture, giving the name to the form

The Dry or Atrophic Form

The dry or atrophic form of the disease appears if the degeneration of the nerves and of the muscles dominates the picture There is more or less marked paralysis, especially in the legs less frequently in the arms, rarely in the trunk muscles, involvement of the cranial nerves is not common, the mind remains clear With extensive paralysis and atrophy of the leg muscles, there is a peculiar gait—only with difficulty is the foot raised from the ground, the toes hanging down weakly, and the foot is set down stampingly With extensive paralysis and atrophy of the muscles of the forearm and hand the hand hangs limply There are disturbances in sensation formication and burning sensations and decrease in sensation The muscle reflexes are lost, and the electric excitability of the muscles is lost, commonly the motor disturbances are symmetrical The paralysis may become so marked that the patient is bedridden

The Wet or Hypertrophic Form

The wet or hypertrophic form may develop from the atrophic form and while the paralyses are not so marked, there is always a distinct weakness in the legs But here, the outstanding features are on the part of the *heart*, which dominates the disease picture, and there is *edema* and serous effusion into the pericardial sac and into the serous cavities The pulse is accelerated and may reach 120 per minute the cardiac dullness is extended especially toward the right The patient complains of palpitation, especially in the evening and at night, pain in the region of the heart, which may be severe, and shortness of breath The cardiac insufficiency may be extreme, and the urinary excretion may be markedly reduced

The Acute Pernicious or Acute Cardiac Form

The acute pernicious or acute cardiac form may develop suddenly in an apparently healthy person or it may develop from the *rudimentary form*, and is not as rare as formerly supposed This is the most dangerous form and may cause death within 24 hours, especially in young persons

In addition to the symptoms noted for the other forms the cardiac weakness amounts to more or less complete cardiac failure There is edema and

effusion into the serous cavities, and all of the cardiac symptoms of the wet form are much more marked, on percussion, there is marked dilatation, the pulse may go to 140 and be scarcely perceptible the blood pressure is markedly lowered, and there may be complete suppression of urine The subjective symptoms are greatly increased There is marked dyspnea, precordial distress, and severe cardiac pain so that the patient cries out and grasps at the cardiac region often for hours With increasing cyanosis, the patient may die of cardiac collapse, remaining conscious to the end

The Chronic Cardiac Form, or the Beriberi Heart

The chronic cardiac form, or the beriberi heart is the form so commonly seen in temperate climates and which has come to be more frequently recognized in recent years

Vitamin B_1 deficiency plays an important part in chronic nonvalvular heart disease, especially in alcoholics * in the Tropics as well as in the temperate zones It is a prominent cause of cardiac failure without any of the usually recognized causes of heart disease Weiss says that "alcoholic beriberi" occurs in drinkers of whiskey and gin less frequently in beer drinkers He says that the "beriberi heart" is not so uncommon in the United States as frequent as 1 in 160 medical admissions in a large charity hospital It is often mild

Eustis (1942) cites the case of a 39 year old white man who used alcohol to excess He had edema of the ankles dyspnea poor response to the cardiorespiratory test, and a venous pressure of 230 mm of water The electrocardiogram showed the QRS waves slurred in the second lead, the T wave low in the second lead, and inverted in the third lead which was interpreted as "definite evidence of myocardial disease" He thinks such cases are more frequent than suspected

DIAGNOSIS

The characteristic symptoms are pretibial edema exhaustion, weakness in the legs decrease in sensation in circumscribed areas of the legs, pain on pressure on the muscles of the calf of the leg the characteristic gait, loss of the patellar reflex, palpitation of the heart and rapid pulse The electrocardiogram is not characteristic though it usually shows myocardial disease negative T waves in the first lead and slight alteration of the ventricular complexes This with a history of coming from a country where polished rice is the principal article of diet or from one of the localities where white wheat flour is the principal article of diet or in an alcoholic, will enable one to make a diagnosis Adrenalin reduces the blood pressure in beriberi as it stimulates the heart, but further dilates the already dilated peripheral arterioles This has been suggested as a diagnostic measure in the cardiac form but it must be used with caution A therapeutic trial of vitamin B_1 is an aid in diagnosis

*Vitamin B_1 deficiency is now recognized as an important factor in acute alcoholism and in delirium tremens and large doses of this vitamin are now included in the treatment of these conditions

PROGNOSIS

Formerly the disease took a heavy toll in morbidity among labor groups and the mortality was a not unimportant feature With better understanding of the prevention and treatment of the disease neither morbidity nor mortality need be important factors *The usual cause of death is cardiac failure* as in the *acute pernicious form*

While proper treatment will quickly relieve the serious symptoms of the disease it must be borne in mind that the regeneration of the degenerated nerves and muscle fibers takes considerable time so that the return to normal is a relatively slow process extending over a period of months or longer

PROPHYLAXIS

With the development of our understanding that the disease is due to a dietary deficiency there should be no problem in prophylaxis among laboring groups and among people in general There still remains the occasional case of the individual who has an abnormal dietary regime imposed by himself In the case of the alcoholic the method of prevention is obvious but failing *the reduction of the intake of alcohol a regular intake of vitamin B_1* or preferably large doses of the multivitamin preparations—not in or with the alcoholic drink as suggested by some sources a few years ago— is the rational prophylactic procedure A balanced diet with sufficient meat dairy products legumes and other vegetables will prevent the disease In the Philippine Islands the disease was prevented and cured among the Philippine Scouts by the addition of rice polishings (tiki tiki) to the diet Of course other improvements in the diet were instituted

For persons who especially like a rice diet and for those who use the rice diet in treatment of hypertension there is now available a form of white rice in which all of the vitamins and minerals are retained

TREATMENT

Just as we now understand that dietary deficiencies are not single and pure so we understand that beriberi is often mixed with one or more of the other dietary deficiencies So while vitamin B_1 is the typical and fundamental deficiency in beriberi and vitamin B_1 is to be given in large doses in the beginning of treatment it must be borne in mind that the condition is often associated with other dietary deficiencies and the other vitamins are to be given along with vitamin B_1 This is in keeping with the trend toward using multiple vitamin therapy in the deficiency diseases Vitamin B_1 is given in doses of 20 to 50 mg per day in divided doses It may be given subcutaneously in the dry form but it is given intravenously in the wet form It is best given intravenously in the early days of treatment especially in the *acute pernicious form* in divided doses Strychnine is indicated in the cardiac

failure* and venesection has been used with good results in extreme cases Adrenalin is contraindicated In the *wet form* diuretics are indicated and a high protein diet in the form of some of the intravenous preparations When the acute symptoms are controlled multivitamin therapy is frequently indicated In addition bed rest a balanced diet with high protein content and correction of the patient s dietary habits are important factors

INFANTILE BERIBERI

Manson thought that beriberi could be due to some microorganism living in the soil in the house or in the ship occupied by human beings and under certain conditions of moisture and temperature could grow and produce a toxin which caused the disease He quoted Hirota s observation that 52 infants nursed by beriberic mothers developed beriberi and did not respond to medical treatment but rapidly improved when placed on artificial feeding or nursed by a healthy wet nurse But Manson thought the children must have been poisoned by some chemical substance and were not infected with a germ †

At one time infantile beriberi caused over 1/ of the infant mortality in the Philippine Islands The Report of the Committee on Beriberi in the Philippine Islands in 1928 says that there are 16 500 infantile deaths annually from this disease i e 28 1 per cent of all infantile deaths in that country

The disease is more serious in infants than in adults with marked prominence of the effect on the heart

Congenital beriberi is rare—the mothers have beriberi Van Gelder and Darby (1944) cite Mata s case of an infant 3 days old The child was cyanotic dyspneic and in apparent pain One hour after injection of 10 mg of thiamine the baby was free of pain They say that in the congenital form the electrocardiogram shows sinus tachycardia right axis deviation and complexes of low voltage in all leads interpreted as definite evidence of myocardial disease They say further that congenital idiopathic hypertrophy or status thymicolymphaticus may be congenital beriberi and suggest that infants with a large heart and no congenital or valvular lesion should be given large doses of thiamine parenterally

The course of *infantile beriberi* is somewhat different from beriberi in adults The *acute form* resembles a tonic spasm with cyanosis and complete cardiac insufficiency The child is suddenly taken sick with loud screaming groaning and hoarseness and may die in the first attack In the *chronic form* the disease begins with vomiting followed by constipation restlessness cardiac insufficiency and edema of the legs When the milk is changed the symptoms frequently disappear in a few days

Vitamin B_1 is given in doses of 5 to 10 mg daily in divided doses

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*Coramin should be of value in the treatment of the cardiac failure in beriberi There are reports of its use in the Japanese literature but I have not found any of these articles or abstracts of them in the United States I have included one reference with the hope that someone may be familiar with the report

†In retrospect especially for those of us who had the pleasure and the privilege of studying with Manson it is surprising that he did not at once grasp the implication of this situation It confirms the point that we could not grasp the situation regarding the part played by the minute quantities of the substances later known as vitamins

Epidemic Dropsy—It is quite definitely agreed that epidemic dropsy is not beriberi One theory is that it is caused by the seed of *Argemona mexicana*, which is toxic, mixed with he mustard seed in regions where mustard seed oil is used in cooking There is much in favor of the theory that it is an infection low fever, redness and swelling of the joints, rythema, and, after a few weeks, skin lesions (bean sized nodular or wart like lesions which bleed easily), and anemia Edema and cardiac symptoms are prominent features

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*No effort has been made to give anything like an extensive bibliography only the publications which have been of special use in preparation of this chapter are noted and acknowledgment is made of the value they have been—E. R. W

CHAPTER 62

PELLAGRA

Roy Edwin Butler

DEFINITION

Pellagra is a dietary deficiency disease due to the failure to ingest, absorb or utilize niacin or its precursors and is characterized by dermatitis stomatitis, diarrhea, and mental disturbances It is usually associated with deficiencies of other components of the B complex such as thiamine and riboflavin and with the lack of protein of good biologic quality

CAUSAL AGENT

In earlier descriptions of pellagra it has been customary to outline the various theories which have been advanced as to the etiologic agent of the disease However, since Goldberger (1926) pointed out the fact that pellagra arises as the result of a dietary deficiency there has been relatively little argument concerning other possibilities Perhaps the most discussion has centered around the question of the exact identity of the factor or factors the lack of which is responsible for the disease The factors were known to be present in yeast and to be water soluble and heat stable

With the announcement by Elvehjem (1937) that nicotinic acid (niacin) would cure black tongue in dogs, it was thought that the pellagra preventive factor had been found However, the administration of this new vitamin to pellagrins did not always cure all of the signs and symptoms associated with the disease Sebrell and Butler (1938) demonstrated that signs formerly associated with pellagra sine pellagra, namely, fissures at the angles of the lips, glossitis and increased sebaceous deposits about the nose, were due to a deficiency of riboflavin (B_2), and the condition was called *ariboflavinosis* This condition would develop in the presence of adequate nicotinic acid and could not be cured by the administration of that vitamin but could be produced by a deficiency of riboflavin and, when developed could be cured by the administration of riboflavin Goldberger (1925), Wheeler (1933) and Stannus (1912) all had associated this condition with pellagra

Peripheral neuritis was seen often as a part of the picture of pellagra and was considered to be due to lack of the pellagra preventive factor However, the treatment with niacin did not always cure the neuritis and it was necessary to treat with thiamine in order to effect a cure With a diet adequate in niacin and riboflavin but deficient in thiamine, a peripheral neuritis would develop which could be cured by the administration of thiamine

Sebrell and Butler (1939) stated

"It, therefore, appears that we should revise our concept of clinical pellagra in that the condition may be a mixture of symptoms from three different deficiencies, namely, nicotinic acid, riboflavin, and thiamine chloride,

and that any one may occur alone or in combination with any other. Therefore in order to avoid further confusion it is suggested that the diagnosis of pellagra should be confined to that syndrome which responds to nicotinic acid, namely skin lesions, gastrointestinal lesions, stomatitis and mental disturbances, while peripheral neuritis which responds to thiamine chloride should be diagnosed as beriberi, and the lesions described in this paper which respond to riboflavin require a new designation since their nature has not been hitherto recognized. We have suggested the word ariboflavinosis for this purpose. Where the clinical condition is characterized by the simultaneous presence of more than one of these syndromes, a diagnosis of a *multiple deficiency* is indicated."

This indicated that pellagra frequently developed as the result of a *multiple deficiency*. It was to be noted that the food sources deficient in niacin were also deficient in riboflavin and thiamine, which accounted for the tendency to attribute the disease to one factor. With the development of the crystalline vitamins it was possible to prepare diets deficient in either factor or both and prove on human subjects the symptoms and signs associated with the lack of each.

There has been an almost constant association of the disease with people consuming a diet of which corn (maize) contributes a good share of the calories. Some had theorized that the corn had insufficient protein, but later it was shown that the protein content of corn seemed to be as good as that of other cereals, the consumption of which was not associated with pellagra. Later it was thought by Swaminathan (1938) that its low niacin content was responsible, but it seems that some corn has a very good niacin content. Recently Krehl (1946) has suggested that "the presence of corn in a synthetic low protein diet alters the dietary nicotinic acid and tryptophane requirement of the growing rat." Still more recently Woolley (1946) has reported that he has extracted from corn a pellagragenic factor which, when added in rather small quantities to an otherwise nonpellagragenic diet, will produce the disease in animals. These last 2 reports are of considerable interest, and their application to human dietary studies may be most illuminating. It is quite certain that the etiology of pellagra is not entirely clear as yet, but it does appear that great strides have been made, and it is equally certain that the application of the present knowledge would almost entirely eliminate this scourge of the undernourished and underprivileged. The presence of endemic pellagra in any community or country indicates a lack of appreciation or application of the principles of public health nutrition which have been clearly elaborated and demonstrated.

Predisposing Causes

Food Supply.—Pellagra and poverty have been closely associated in the minds of all concerned since the disease was first described. However, it is necessary to qualify this to some extent, for in some parts of the world poverty is rampant and the diets seem woefully inadequate and yet the disease is not common. It seems that not only must the diet be poor, but it must have a certain quality of poorness which is responsible for the disease. With eco

nomic reverses the quality of the dietary becomes progressively worse as the protective foods are replaced by cheaper foods consumption of which will allay hunger and furnish energy Almost always the cereal content of the diet becomes larger displacing fresh meats milk eggs fresh vegetables and fruits which are more expensive and more difficult to obtain Even during times of apparent prosperity with high prices and good wages one can find many individuals on low fixed incomes from pensions wages or relief whose condition steadily deteriorates because of the poor quality of the diet they can procure This may set up a vicious cycle in that they are less able to provide for themselves and necessarily the diet becomes worse until they become public charges Surveys of the population would be of great service in finding those individuals or groups most likely to succumb to dietary deficiencies Such a course of action has been recommended from time to time but seldom carried out The incidence of pellagra can only be approximated in many countries having high health standards which seems somewhat paradoxical The evaluation of the nutritional status of patients in the charity outpatient clinic and hospital wards can show what is happening in that segment of the population which is particularly vulnerable to deficiency diseases

Sebrell (1945) stated that 1 303 deaths from pellagra were reported from the United States in 1943 He believed that the mortality should not be over 3 per cent with the newer methods of treatment This would give an estimated 43 400 cases of pellagra However there were probably a much larger number with mild symptoms

Alcoholism —It seems that alcohol addiction and pellagra are quite closely associated and it is now held that this is true because of the lowered food intake which at times accompanies immoderate ingestion of alcohol The alcohol addicted individual with a poor economic state will prefer alcohol to food As he continues to drink without eating a proper diet there will be a greater need for the effect of alcohol to hide his increasing ill feeling Many alcoholics have a good dietary available but have a preference for the alcohol and because of that many become severely deficient Anything that interferes with the intake of a proper diet or its absorption may be responsible for the development of dietary deficiencies

Increased Demands —Physiologic demands for specific nutrients are increased during pregnancy lactation and adolescence and this increase is met by additional allowances in the diet The association of these stress periods with pellagra may be coincidental but in view of the frequency with which signs of B complex deficiencies are encountered in these groups it is probable that they are the most susceptible of those subsisting on a minimal diet Every effort should be made to ensure an adequate diet for these groups inasmuch as there may be long range deleterious effects upon the individual or their offspring from a diet lacking in certain specific nutrients

Immediately prior to or following surgical operations it has been a common practice to administer large amounts of parenteral fluids containing glucose as a source of energy From this procedure the body may suffer considerable depletion of specific nutrients thus hindering the recovery of the

patient It is now the practice in many surgical clinics to administer specific nutrients including protein hydrolysates with the parenteral fluids in order to simulate as closely as possible the recommended intakes of those substances The value of such steps depends upon the condition of the patient at the beginning of the treatment the course of the patient with regard to fever and complications and the length of time necessary before the resumption of an adequate diet

Defects of Absorption —Improper mastication because of poor teeth or ineffective dentures may not prepare the food properly for digestion Gastro intestinal tumors or diarrheas may interfere with absorption thereby resulting in deficiencies Hepatic dysfunction *may contribute materially to failure of* absorption or utilization of the specific nutrients This has been shown to be particularly true in the case of schistosomiasis involvement of the liver which *is frequently followed by the appearance of deficiency diseases This* is of particular importance in Egypt where the infestation with Schistosoma is so widespread

Voluntary Inadequate Intake —There are several methods of voluntarily restricting the diet so that severe deficiency results even though there may be plenty of good food available Here one may be able to bring about good results through proper education of the patient

It is suggested that iatrogenic deficiency may result from the prescription of poor diets over long periods in the mistaken belief that some type of unbalanced diet will be corrective for some organic diseases A common offender was the diet for hypertension which materially reduced the intake of red meat eggs and other protein foods Unbalanced diets used in the treatment of peptic ulcer may result in serious deficiency status In all fairness it should be stated that patients placed on a diet may fail to return for further treatment and continue on a regimen which the doctor intended should be pursued for a short time only There have been many fads which have encouraged the use of inadequate diets for various purposes Many of the reducing diets have been grossly deficient but these seldom do much damage for they are usually not adhered to for long periods of time and the enthusiasm of the reducer wanes with his increasing desire to eat

Improper selection of foods in the dietary is another factor which is of considerable importance and may result from dislikes for certain classes of foods Individuals who prefer a meat free diet have to be especially careful in the selection of foods in order to ensure an adequate intake People living alone and preparing their own meals are more likely to have their dietary restricted because of the difficulties of preparing proper food for one person They are likely to fall into a routine of foods easily prepared or preserved from one meal to the next and fail to have a well balanced dietary

Sex —Sydenstricker (1941) in a study of 660 cases found 32 per cent of the patients were men and 68 per cent women The same percentages as these were found by Ruffin and Smith (1941) in a study of 465 cases It is a defi

nite possibility that under certain conditions in various parts of the world the ratio between men and women may be considerably altered There is a sex distribution of schistosomiasis in Egypt with more men attacked than women This infection has been associated with pellagra and it would be expected that the incidence of both diseases would be higher in men in that country

Age—Goldberger had considered endemic pellagra as largely a disease of infancy and childhood i e from 2 to 15 years of age Dodd (1941) reported from the Pediatrics Service of the Vanderbilt Hospital that 13 per cent of all admissions diagnosed as pellagra were children under 15 years of age Ruffin and Smith (1941) stated in their series of 465 cases that 10 per cent were from infancy to 19 years of age Sydenstricker (1941) noted a wide age distribution from 5 to 92 years and found 60 per cent of the patients were in the age group from 21 to 50 years

Race—Cases are found about equally divided between the white and Negro races in the United States This proportion may vary in different parts of the country as is evidenced by Sydenstricker s (1941) report of 57 per cent white and 43 per cent Negro in his series It is quite evident that much depends upon the food patterns of races and if various races living within a country have similar food habits the proportion of cases should be quite similar unless there are other factors which affect the dietary unduly

Occupation—The disease has been most common in rural populations in *most parts of the world In the United States it has existed to the greatest* extent in the rural and mill village population of the South It is to be noted that the farmers of the area produce cotton and tobacco to the exclusion of foodstuffs Every effort has been made in encouraging farmers in the production of more of the protective foods for their own consumption In some of the European countries the farmers producing protective foods have had to sell them as their cash crop and resort to the poorer cheaper foods for their own subsistence with the result that malnutrition has been common Institutions for the care of orphans the aged the psychotic and criminals have in the past been guilty of providing insufficient food for the inmates however much has been done to safeguard the interests of these inmates With the prospects of higher prices for food there will be a need for retrenchment on expenses and food too often is an item which suffers This may again lead to a lowering of the standards of the institutions with resulting ill effects upon the inmates

CLINICAL SYMPTOMS

The description of pellagra by Casal (1762) covered most of the important points to be observed in the diagnosis of cases of florid deficiency With the realization of the importance of recognizing the deficiency before it reached the full blown state attempts have been made to find signs and symptoms that would be indicative of an earlier stage so that the appropriate treatment could be instituted Goldberger (1926) had stated that without the typical dermatitis the diagnosis could not be made with any degree of certainty Much

work has been done in the laboratory endeavoring to find tests which would be of value in establishing or corroborating the diagnosis

Even at the present time the classic triad of dermatitis diarrhea and dementia is the most acceptable criterion of the presence of the disease Certain signs are now considered as presumptive evidence of deficiency but further work is needed before accepting them as incontrovertible evidence However the presence of presumptive signs in those whose dietary intake is *adjudged to be inadequate should* indicate the need for therapeutic supplementation of the diet

The *therapeutic trial with a specific nutrient has proved useful in some* doubtful cases However the results are frequently very difficult to evaluate for the appetite may be stimulated to a better dietary intake producing an improvement that cannot be construed as being associated with any specific nutrient If specific nutrients are given in the form of crystalline vitamins certain signs and symptoms may be cleared without restoring the individual to nutritional health It is also difficult to maintain all other factors exactly *and a change in activity or unconscious improvement of the diet may ma*terially alter the condition of the patient It is also difficult to be objective in evaluating the signs and symptoms as the appraisal of the patients by several observers on successive examinations may vary a great deal To be desired are objective criteria which may be evaluated the same by all observers

The seasonal incidence of the disease should always be kept in mind for it was noted quite early that the first signs and symptoms usually appeared at about the same time of the year and might be present for several years in succession Such periodicity is explained by the fact that the diet worsened during the winter months as the supply of fresh vegetables diminished and recourse to more stable foods with lower vitamin content was necessary With the coming of the summer there became available the products of the garden and an increase in the vitamin content of the diet Another important factor was the custom of slaughtering animals for food in the fall and preserving a good part of *the meat with salt for use in the late winter and spring* Also with the coming of spring activities became accelerated with the preparation of the fields for the new crops and coincidentally with this was the increase in daily temperatures because of the accentuation in the power of the sun s rays Thus there was a decrease in the vitamin content of the diet and an increased demand by the body for a more nutritious diet which led to the appearance of the deficiency disease

In discussing *the signs and symptoms of pellagra it is to be noted that* there is no definite order of occurrence of the manifestations of the disease The chronologic order may also be quite varied and one or more signs or symptoms may be present for quite long periods of time before the appearance of others Frequently there has been confusion in interpretation of the appearance of the disease because of the presence of *concomitant disease* Also the fact that deficiencies almost always were multiple further complicated *the picture* The signs and symptoms will be discussed individually

Dermatitis

From the first the dermatitis has been the most pathognomonic sign of the disease and the effect of irritative agents upon exposed parts of the body was considered significant The lesion itself can well be looked upon as the response of the skin to an irritation and the amount or degree of involvement possibly depends upon the extent of the deficiency and the intensity of the stimulus The dermatitis may range from a mild erythema to a bullous type of lesion

Following the appearance of erythema there is pigmentation and desquamation which may be of a more or less chronic nature At times a secondary infection may occur and mask the diagnosis and local application applied to the area may result in improvement of the condition These lesions do not necessarily arise from exposure to the sun but may be the result of irritation of strong soaps or sweat as is shown by the involvement of the scrotum and vulva The basal lesions also may be made worse by the use of strong antiseptics or medications which have been applied in the mistaken belief that an infection is present

The *distribution of the lesions has always been noteworthy and frequently* assists in arriving at the correct diagnosis It has already been mentioned that the lesions are more commonly seen on parts of the body exposed to the sun

In addition the bilateral symmetry of the lesions is very striking Unilateral lesions of the characteristic type may occur but this distribution is not nearly as common

On the extremities there is usually involvement of the extensor surfaces although at times the flexor surfaces may be affected In addition the lesions are common over or adjacent to joints—more specifically the elbows wrists knees and ankles Occasionally the region at the base of the neck may be involved and the descriptive name of collar of Casal is applied to the appearance of lesions here since it was described by Casal in 1762 The lesions of the scrotum and the vulva frequently are mistaken for a fungus infection because of the spread to the thighs and the pigmentation which is commonly associated with that condition Both sites may show ulceration and prove to be quite painful

The face may show the typical lesion on both cheeks extending across the bridge of the nose in a butterfly pattern which may simulate lupus erythematosus There is at times an involvement of the sebaceous follicles of the skin of the nose and forehead which are filled with hardened plugs and stand out from the surface like small columns A skin so involved feels very coarse and rough to the examining finger

Glossitis

One of the most characteristic signs of pellagra has been the glossitis and it is probably the most constant manifestation In the presence of a normal appearance of the tongue the diagnosis is extremely difficult to make

with any assurance The tongue is usually somewhat thickened and has a beefy red color with a smooth surface due to the loss of both the fungiform and filiform papillae There may be a firmly attached white patchy fibrinous coating overlying the erythema

Saliva may drool from the mouth Casal (1762) described a dirty gray coated tongue and a fetid breath Undoubtedly there are times before the degenerating papillae have been cast off when the tongue would have that appearance With the casting off of the coating there would be revealed the typical smooth beefy red tongue

The loss of papillae usually begins at the tips and sides of the tongue and progresses until the whole surface has the same appearance Dental impressions along the sides of the tongue may be quite prominent The tongue burns and feels sore and makes eating difficult if not impossible which interferes with recovery even though a therapeutic diet is offered With the institution of proper therapy the papillae reappear beginning at the middle of the dorsum and spreading out to the sides and anteriorly until the surface is again covered and the pinkish color restored with an overlying delicate whitish covering denoting a normal tongue

Butler (1943) called attention to the difficulties of differentiating between the tongue of ariboflavinosis and that of niacin deficiency and suggested the use of clinical trials with each of the vitamins in order to reach a decision The buccal mucous membranes and gums may also be erythematous and appear inflamed

The changes of the mouth are said to be somewhat representative of the appearance of the remainder of the gastrointestinal tract With the inflammation of the stomach and intestines a diarrhea is not uncommon which results in increasing difficulty in the absorption of nutrients It has been thought that preceding the inflammation there is a considerable degree of atrophy of the mucosae which in the stomach may have something to do with the disappearance of free hydrochloric acid which is so common in pellagra Under treatment the achlorhydria may disappear and a normal acid content be found on examination

Fissures have been described at the angles of the lips which began at the vermilion border and extended out on to the skin for ½ to 1 cm When occurring alone this sign had been responsible for the term pellagra sine pellagra The dermatologists had called this condition *perleche* and thought it to be due to a monilial infection However Sebrell and Butler (1938) showed that the condition was due to a lack of riboflavin in the diet These fissures were seldom painful and ordinarily did not bleed but on healing would leave a nonpigmented scar which would persist It has been reported by Smith (1940) that pyridoxine (vitamin B_6) will cure some of these fissures It should be kept in mind that even on a riboflavin deficient diet there may be periods of remission in spite of the fact that specific therapy has not been given Toothless people and those with ill fitting dentures may have a fold at the angles of the lips which show maceration and erythema difficult to differentiate from the fissures of ariboflavinosis

Kruse (1942) has described changes in the papillae of the tongue that can be seen with the biomicroscope which he stated were diagnostic of niacin deficiency at a much earlier stage than by any other criteria He observed that there was first a swelling and engorgement of the papillae which was followed by atrophy and desquamation resulting finally in the smooth red tongue These findings have not been accepted by all workers in the field and undoubtedly additional work will clarify the situation

Diarrhea

The diarrhea usually makes its appearance fairly late in the disease and consists of watery stools occurring 2 or more times daily This condition may be severely debilitating and interferes with the proper absorption of food from the already handicapped gastrointestinal tract In addition if severe it results in a certain degree of dehydration of the patient

Weakness

One of the early symptoms is a sense of weakness which becomes more marked with the progress of the disease The patients show a disinclination to engage in purposeful activity which probably accounts for an apparent lack of ambition or desire to improve their condition With proper treatment there is a return of strength and improvement in the sense of well being Spies (1943) made a study of the rehabilitation of the chronically malnourished which showed what can be done to change individuals from an economic loss to an economic asset

Weight Loss

Another sign which usually appears early in the disease is a decrease in weight which usually parallels the severity of the condition Occasionally pellagrins will be obese but show the other typical signs of the disease It should be kept in mind that obesity is not always a sign of good nutrition and may be the result of overeating of foods low in specific nutrients in order to attempt to satisfy the needs of the body Progressive weight loss with a history of a poor dietary should make one suspicious of a subclinical deficiency if all other common causes for loss of weight have been ruled out It should also be kept in mind that there may exist concomitant deficiency disease with tuberculosis ancylostomiasis malaria neoplasia schistosomiasis and other diseases

The geriatric patient showing marked weight loss with a poor dietary history and without demonstrable organic lesion of a serious nature may present a problem that seems more or less hopeless If a defeatist attitude is adopted because of the age and frailty of the patient the foregone conclusion will soon be realized However if a constructive approach is taken there is an opportunity to achieve some rather surprising results Such patients present a picture that is all too common and may indicate subclinical to obvious deficiencies which may include pellagra Everyone is familiar with the elderly patient

appearing older than the stated age showing signs of definite loss of weight wrinkled skin with loss of turgor moderate to marked anemia feebleness and uncertainty of movements the tongue smooth and pale or reddened and having many querulous complaints and loss of hope and ambition Careful study of the case fails to show serious organic reasons for the decline A superficial dietary history secured from the patient may be misleading for he frequently will make it appear that the diet consumed is quite good However *the taking of a detailed dietary history will* reveal inadequate variety of foods and insufficient quantities Corroboration of the true state of affairs may be secured from those living in the same house The treatment of the obvious deficiencies and the consumption of an adequate diet may work wonders with the patient Hospital care which permits close scrutiny of the dietary intake and the progress of the patient will usually result in marked improvement whereas on returning home they are prone to follow the same course that was responsible for their condition More careful study of the dietary problems of the geriatric patient may assist materially in demonstrating many facts about their absorption and utilization of foods which are not known at the present time The problem is a challenging one and promises good returns for the efforts spent in its solution

Dementia

The dementia of pellagra usually is very insidious in its onset and may *progress to a psychotic state which may be so severe as to necessitate the* incarceration of the patient in a mental institution It was reported that about 1/4 of the admissions to mental institutions in Egypt were the result of malnutrition and a goodly percentage of these had pellagra In the early stages the patients show lassitude uncertainty lack of purpose forgetfulness and confusion This may then progress to actual psychosis with disorientation delusions of persecution and lack of insight Under proper treatment the condition slowly regresses but there may not be complete recovery

Jolliffe (1940) described an acute deficiency of niacin in the central nervous system which he labeled nicotinic acid deficiency encephalopathy This condition was characterized by stupor cogwheel rigidity and appearance of the sucking reflex He reported rather sensational success with these cases when they were treated with adequate doses of niacin and niacinamide In a series of cases treated with hydration and supportive treatment there was a mortality of 80 per cent In a comparable series treated with large doses of nicotinic acid the mortality was reduced to 13 6 per cent

Cleckley (1939) described a series of cases of stupor with no organic lesions to explain their condition and they responded surprisingly well when sodium niacinate was given in doses of 100 to 300 mg These patients usually *presented a very poor* dietary history without typical lesions of pellagra The hebetude grading into stupor was thought to be indicative of severe acute pellagra and the administration of niacin was held to be lifesaving

TREATMENT

In treating pellagra it must be kept in mind that a multiple deficiency disease has to be coped with, and any measures directed toward the supplying of single vitamins will fall short of the desired goal It also must be kept in mind that pathologic processes may be interfering with the absorption or utilization of the nutrients given therapeutically Spies (1935) made a significant contribution when he demonstrated, with a series of cases, that it was necessary to do more than offer a good diet to the patients, for it was essential that the food be ingested even though it required an increased staff of nurses and attendants He showed that the mortality in severe pellagra could be reduced from 54 to 6 per cent by these means Needless to say, if the food or specific nutrients cannot be taken orally or absorbed from the gastrointestinal tract, it will be necessary to administer them parenterally in proper form

Almost all writers on the subject of the treatment of pellagra from the earliest days have emphasized the importance of a good diet if the treatment were to be successful At the present time such a good diet would satisfy the Daily Recommended Allowances of the National Research Council and additional amounts of foods rich in the B complex, in appropriate proportions, should be given

Foods that are known to be therapeutically active against pellagra are whole grain cereals, milk, liver, red meat, fresh vegetables nuts and yeast In the case of milk, its effectiveness certainly does not seem to be measured in terms of its niacin content, for that has been demonstrated to be low but Goldberger (1927) clearly showed its value as a pellagra preventive These foods should be emphasized in the diet and have been traditionally used with good results

Elvehjem (1937) showed that nicotinic acid (niacin) was effective in the treatment of canine black tongue, and soon afterward it was demonstrated by Fouts (1937), Harris (1937) Smith (1937), and Spies (1938) that it was also effective in human pellagra It was soon noted by Sebrell and Butler (1938) that nicotinic acid (niacin), when given even in small doses to certain people, would result in marked flushing and burning of the skin which was especially marked over the face, points of the shoulders, elbows, and knees and occasionally a sense of substernal depression This reaction would occur within 15 minutes and would last for 30 to 45 minutes, and, aside from the unpleasant sensation apparently had no deleterious effect The sodium nicotinate which was the injectable form also had a similar action With the introduction of the nicotinamide (niacinamide), this effect was not noted and there seemed to be no loss in the therapeutic effectiveness, this is the preparation in most common usage at the present time Coramine, the diethylamide of nicotinic acid, has also proved to be effective in treatment

The treatment of pellagra depends upon the state and severity of the disease and the complications that may be associated with it There have been

several classifications suggested to convey some impression of the various stages or forms of the disease It is realized that any such classification must be arbitrary and must depend upon definition for its validity At the risk of oversimplification it is suggested that there be 3 subdivisions (1) the prophylactic preventive or subclinical (2) the *moderately severe* and (3) the severe

The Prophylactic Preventive or Subclinical Pellagra

In defining this subdivision it is suggested that there be included those individuals whose dietary appears to be inadequate but who manifest no suggestive or presumptive signs of pellagra Also included are those individuals subsisting on an inadequate diet who manifest *suggestive or presumptive* signs of pellagra but for whom a definite diagnosis of the deficiency cannot be made *This subdivision is probably the most important because it applies* to a much larger group of individuals than either of the other groups Goldberger (1927) stated It is probable that in each year for every death attributed to the disease there are fully 20 persons with clearly recognizable attacks and probably as many more with debility from the same cause but not definitely marked as such ' It is particularly necessary in dealing with this group to try to improve the dietary in every way possible Education of these individuals along the lines of proper nutrition and how they may best secure it is of fundamental importance In rural areas it may be necessary to en*courage the planting of gardens and keeping of cows and the use of milk* products In the city it may mean change of food habits instruction as to *the nutrient values of various foods and the discontinuance of the use of* alcohol

In providing the proper diet it is essential that the Daily Recommended Allowances of the National Research Council be met as nearly as possible

It is obvious that it is necessary to know the nutrient content of the foods used and it is hardly safe to apply the values secured in one locality to the foods of other areas The entire aim is to furnish the required nutrients in *the required amounts and proper proportions* Generally speaking the foods previously mentioned would be effective in preventing deficiencies of niacin In case it is impossible to *improve the dietary one might have recourse to a* rich source of the B complex such as brewers' yeast ½ to 1 ounce daily or some of the multivitamin preparations so widely advertised *at the present* time It becomes the responsibility of the medical profession and the public health authorities to know whether the people of a community are subsisting on inadequate diets and to provide suitable remedies to overcome such deficiencies

Moderately Severe Pellagra

In this subdivision are the patients that have signs and symptoms upon which a definite diagnosis *can be based The patient has characteristic skin* lesions sore mouth weakness and loss of weight There may be diarrhea and mental changes However he is still *attempting to do his work and is not*

TABLE XXX RECOMMENDED DIETARY ALLOWANCES REVISED 1945
(AMOUNTS PER DAY)
(From Food and Nutrition Board, National Research Council)

	CALORIES	PROTEIN (GM.)	CALCIUM (GM.)	IRON (MG.)	VITAMIN A (I.U.)	THIAMINE (MG.)	RIBOFLAVIN (MG.)	NIACIN (NICOTINIC ACID) (MG.)	ASCORBIC ACID (MG.)	VITAMIN D (I.U.)
Man (154 lb., 70 kg.)										
Sedentary	2500	70	0.8	12	5000	1.2	1.6	12		
Moderately active	3000	70	0.8	12	5000	1.5	[illegible]	1	75	
Very active	4 00	0	0.8	12	5000	2.0	6	0	5	
Woman (123 lb., 56 kg.)										
Sedentary	2100	60	0.8	12	000	1.1	1.5	11	0	
Moderately active	2 00	60	0.8	12	5000	1	1.6	1	0	
Very active	3 00	60	0.8	1	500	1.5	0	15	0	
Pregnancy (latter half)	00	8	1.5	15	60 0	1.8		18	1 0	4 to 800
Lactation	3000	100		15	8 00	2.0	3.0	0	150	400 to 800
Children up to 12 yr.										
Under 1 yr.	100/2 lb. (1 kg.)	3.5/2 lb. (1 kg.)	1.0	6	1500	0.4	0.6	4	30	400 to 800
1-3 yr. (27 lb., 13 kg.)	1200	4	1.0	7	2000	0.6	9	6	35	4)
4-6 yr. (42 lb., 19 kg.)	1600	50	1.0	8	500	0.8	1	8	50	400
9 yr. (55 lb., 25 kg.)	2000	60	1.0	10	3 00	1.0	1.5	10	60	400
10-1 yr. (7 lb., 34 kg.)	2500	0	1.2	12	4 00	1.2	1.8	1	5	400
Children over 12 yr.										
Girls 13-15 yr. (108 lb., 49 kg.)	2600	80	1.3	15	5000	1.3	0	13	80	400
16-20 yr. (119 lb., 54 kg.)	400	75	1.0	15	5000	1	1.8	12	80	400
Boys 13-15 yr. (103 lb., 47 kg.)	3 0	85	1.4	15	50	1.5	0	1	0	400
16-20 yr. (141 lb., 64 kg.)	3800	100	1.4	15	6000	1.8	2.5	18	100	400

several classifications suggested to convey some impression of the various stages or forms of the disease It is realized that any such classification must be arbitrary and must depend upon definition for its validity At the risk of oversimplification it is suggested that there be 3 subdivisions (1) the prophylactic preventive or subclinical (2) the moderately severe and (3) the severe

The Prophylactic, Preventive, or Subclinical Pellagra

In defining this subdivision it is suggested that there be included those individuals whose dietary appears to be inadequate but who manifest no suggestive or presumptive signs of pellagra Also included are those individuals subsisting on an inadequate diet who manifest suggestive or presumptive *signs of pellagra but for whom a definite diagnosis of the deficiency cannot* be made This subdivision is probably the most important because it applies to a much larger group of individuals than either of the other groups Goldberger (1927) stated " It is probable that in each year for every death attributed to the disease there are fully 20 persons with clearly recognizable attacks and probably as many more with debility from the same cause but not definitely marked as such " It is particularly necessary in dealing with this *group to try to improve the dietary in every way possible Education of these* individuals along the lines of proper nutrition and how they may best secure it is of fundamental importance In rural areas it may be necessary to encourage the planting of gardens and keeping of cows and the use of milk products In the city it may mean change of food habits instruction as to the nutrient values of various foods and the discontinuance of the use of alcohol

In providing the proper diet it is essential that the Daily Recommended Allowances of the National Research Council be met as nearly as possible

It is obvious that it is necessary to know the nutrient content of the foods used and it is hardly safe to apply the values secured in one locality to the foods of other areas The entire aim is to furnish the required nutrients in the required amounts and proper proportions Generally speaking the foods previously mentioned would be effective in preventing deficiencies of niacin *In case it is impossible to improve the dietary* one might have recourse to a rich source of the B complex such as brewers' yeast ½ to 1 ounce daily or some of the multivitamin preparations so widely advertised at the present time It becomes the responsibility of the medical profession and the public health authorities to know *whether the people of a community are subsisting* on inadequate diets and to provide suitable remedies to overcome such deficiencies

Moderately Severe Pellagra

In this subdivision are the patients that have signs and symptoms upon which a definite diagnosis can be based The patient has characteristic skin lesions sore mouth weakness and loss of weight There may be diarrhea and mental changes However, he is *still attempting to do his work and is not*

TABLE XXV RECOMMENDED DIETARY ALLOWANCES, REVISED 1945
(AMOUNTS PER DAY)
(From Food and Nutrition Board, National Research Council)

	CALORIES	PROTEIN (GM)	CALCIUM (GM)	IRON (MG)	VITAMIN A (I U)	THIAMINE (MG)	RIBOFLAVIN (MG)	NIACIN (NICOTINIC ACID) (MG)	ASCORBIC ACID (MG)	VITAMIN D (I U)
Man (154 lb 70 kg)										
Sedentary	2500	70	0.8	12	5000	1.2	1.6	12	75	
Moderately active	3000	70	0.8	12	5000	1.5	2.0	15	75	
Very active	4500	70	0.8	12	5000	2.0	2.6	20	75	
Woman (123 lb, 56 kg)										
Sedentary	2100	60	0.8	12	5000	1.1	1.5	11	70	
Moderately active	2500	60	0.8	12	5000	1.2	1.6	12	70	
Very active	3000	60	0.8	12	5000	1.5	2.0	15	70	
Pregnancy (latter half)	2500	85	1.5	15	6000	1.8	2.5	18	100	400 to 800
Lactation	3000	100	2.0	15	8000	2.0	3.0	20	150	400 to 800
Children up to 12 yr										
Under 1 yr	100/2.2 lb (1 kg)	3.5/2.2 lb (1 kg)	1.0	6	1500	0.4	0.6	4	30	400 to 800
1-3 yr (29 lb, 13 kg)	1200	40	1.0	7	2000	0.6	0.9	6	35	400
4-6 yr (42 lb 19 kg)	1600	50	1.0	8	2500	0.8	1.2	8	50	400
7-9 yr (55 lb 25 kg)	2000	60	1.0	10	3500	1.0	1.5	10	60	400
10-12 yr (75 lb, 34 kg)	2500	70	1.2	12	4500	1.2	1.8	12	75	400
Children over 12 yr										
Girls, 13-15 yr (108 lb, 49 kg)	2600	80	1.3	15	5000	1.3	2.0	13	80	400
16-20 yr (119 lb, 54 kg)	2400	75	1.0	15	5000	1.2	1.8	12	80	400
Boys 13-15 yr (103 lb, 47 kg)	3200	85	1.4	15	5000	1.5	2.0	15	90	400
16-20 yr (141 lb 64 kg)	3800	100	1.4	15	6000	1.8	2.5	18	100	400

confined to bed This form of the disease can ordinarily be treated with diet alone but especial care must be observed in being sure that the prescribed diet is rich in B complex food and that it is eaten *in the proper amounts* The use of crystalline vitamins and yeast will hasten the recovery and should be used if available

Niacin (nicotinic acid) 150 to 200 mg daily can be used but the patient should be warned of possible uncomfortable reactions It is better to give niacinamide 150 to 200 mg daily and with this preparation no reactions are to be expected At the same time 10 to 50 mg of thiamine and 10 mg of riboflavin should be given daily It is better to give these vitamins in divided doses 4 to 5 times daily inasmuch as large doses given at one time are largely excreted in the urine and their value lost In addition to these it is well to use brewers yeast 1/2 to 1 ounce daily The yeast may be mixed with milk tomato juice or water and is usually accepted better when it has been refrigerated until it is quite cold One may use liver extract preferably the crude form in doses of 75 to 100 c c intravenously in 3 to 5 doses of 20 c c each for 7 to 10 days With the exception of the liver it is expected that all of the needed nutrients may be taken by mouth One may also use wheat germ 250 to 300 Gm or Ventriculin 200 Gm daily One would expect to see a fair degree of improvement in 7 to 10 days if there are no complicating factors interfering with the absorption or utilization of nutrients Failure to improve under this regimen casts some doubt upon the validity of the diagnosis but before discarding it the nutrients should be tried parenterally for 7 to 10 days more Occasionally a patient will be unable to absorb the nutrients when given by mouth but will utilize them if they are given parenterally Restriction of activities is advisable and will speed recovery because there is less demand for energy expenditure Reassurance of the patient regarding his condition is of importance for many may believe that they have a condition which is contagious disgraceful or incapable of cure and knowledge of their condition will relieve their minds

Severe Pellagra

Severe pellagra is the most difficult stage of the disease to treat and may require the utmost exertion on the part of the medical and nursing personnel if the patient is to recover The patient is obviously very ill and demonstrates the major signs and symptoms of the disease such as characteristic dermatitis sore mouth and perhaps diarrhea and dementia He is very weak perhaps prostrated emaciated somewhat anemic and frequently shows evidence of considerable dehydration He may not cooperate with the treatment and may in fact actually obstruct the treatment through apparent lack of interest or *insight into his condition* Food may be refused because of anorexia which may be due in part to the soreness of the mouth, and the pain involved in eating overbalances the desire for food It is in this type of case that the use of parenteral nutrients may be of inestimable value and spell the difference between success and failure in treatment Injectable preparations of the

vitamins are available and can be used singly or combined in what is considered to be the proper proportions for therapeutic use The dosages are substantially the same as used orally in the treatment of the moderately severe group The diet should be liquid or semisolid until the mouth is sufficiently improved to allow the use of solid foods The caloric intake should be fairly high 2 500 to 3 500 calories and contain milk eggs rich meat soups and cereals *As soon as tolerated the diet should be more solid and composed of* foods rich in the B complex

When treatment is first begun it may be necessary to combat the dehydration with physiologic saline until hydration is achieved Sedation may be helpful to counteract the mental excitement and confusion It may be necessary to give blood transfusions if the patient is severely anemic

GENERAL MEDICAL MEASURES

Pellagra may appear as a complication of other diseases such as tuberculosis malaria malignancies intestinal parasitic infestations schistosomiasis following surgical operations during pregnancy and lactation and in other diseases in which there is interference with intake absorption or utilization of the required specific nutrients Every effort should be made to treat adequately the accompanying condition as well as the pellagra This of course presupposes that every effort is being made to satisfy the nutritional requirements

Dermatitis

Secondary infection of the skin lesions may be present and the treatment given depends upon the severity and type of organism Obviously the infection which is superimposed upon a skin surface already weakened and irritated should be treated as mildly as possible for strong antiseptics or germicidal agents may further damage the involved area Hot compresses of hypertonic solutions of magnesium sulfate serve ordinarily as adequate treatment Sulfathiazole ointment 5 per cent or penicillin ointment may be effective Protection of the skin against irritative agents such as strong sunlight or harsh soaps should be observed

Glossitis

If the mouth is sore one may use mild mouth washes several times daily Usually with the proper intake of specific nutrients the mouth improves very rapidly Vincent s organisms which are present in large numbers during the deficiency soon decrease in number as improvement progresses

Diarrhea

One may use the customary agents for control of diarrhea but usually they are not particularly effective Improvement of the nutrition is usually associated with a decrease in the number of stools and a return to more normal consistency If the motile form of *Endamoeba histolytica* is found it is

advisable to begin treatment with the amebicides unless the *condition of the* patient is too critical One must weigh in his mind the condition of the patient the estimated damage due to the presence of the parasites the danger inherent in the drugs and the response to be expected from dietary therapeutics

Dementia

The obviously psychotic patient should be given the same care and consideration that is customarily accorded the mentally ill It is necessary to take into consideration that (1) the psychosis may be entirely due to the pellagra (2) the pellagra may have activated an underlying latent psychosis such as schizophrenia paranoia or manic depressive type (3) the psychosis may have been present and the pellagra *is merely a complication of it*

The patients not yet obviously psychotic should be reassured and if too excitable or nervous may be benefited by mild sedation

Weakness

Restricting the activities of the patient usually has a beneficial effect because of the lessening of the demands upon the body It has been observed on many occasions that the patients who are hospitalized may have a remission of signs and symptoms without the diet being improved This may partially explain some of the seasonal variation of the disease in that the periods of greatest activity correspond roughly with the increased incidence of the disease With the use of the proper dietary therapy there is usually a rather rapid increase in strength and ability to work

Considerable emphasis should be given to the task of instructing the patient about the cause of his difficulty and what should be done about it when he returns home All too frequently these patients on leaving the hospital return to their old dietary either through necessity or by preference often resulting in a recurrence of the disease after a time If possible contact should be maintained either by having the patient report to the physician at regular intervals or by visiting the patients in their homes Economic rehabilitation is difficult but not infrequently is the only real solution to the problem Any amount of good advice about the proper dietary is of little value if the proper foods cannot be grown or purchased

LABORATORY DIAGNOSIS

The laboratory has not been of great value in establishing the diagnosis of pellagra but it has had corroborative significance Much work has been done in the attempt to provide tests that would point out the presence of a *subclinical deficiency or a gross deficiency* but *as yet* such tests can be suggestive only when combined with certain clinical signs or a history of a deficient dietary

The presence of F_2 in the urine by the method of Najjar (1944) has been used as an indicator of a deficiency of niacin in the system The excretion of

the n methyl niacinamide (F_2) in the urine can be determined by the measurement of the fluorescence produced by appropriate treatment of the urine As the deficiency progresses the amount of the F_2 decreases but this does not always indicate the imminence of the appearance of clinical pellagra

Attempts to measure the niacin content of the blood have shown a remarkable constancy in the amount present regardless of the nutritional status of the patient Thus such a measure has proved to have little value in the diagnosis of subclinical or clinical pellagra

The use of load tests has been thought to give some indication of the niacin status of the person tested Perlzweig (1942) showed that the fasting urinary level of total nicotinic acid (nicotinic acid plus trigonelline) was practically the same when comparing normal and apparently deficient groups After fasting urine was collected 500 mg niacinamide were given and the urine collected over a 12 hour period The test showed that those subsisting on the better dietary excreted more of the total nicotinic acid than those on the marginal intake Such a method might be used to good advantage in small groups of patients but obviously it would be of little value for survey purposes

The blood picture is not characteristic but with the disease one may expect to find some degree of normochromic normocytic anemia which in some cases may approach the hyperchromic macrocytic type of anemia

The blood chemistry may show some decline in the serum proteins but usually not of severe degree The albumin fraction is usually more depressed than the globulin

Gastric analysis according to Sydenstricker (1941) frequently shows achlorhydria which may or may not return to normal under treatment

The stools may be watery but seldom show mucus or blood Especial attention should be directed toward the determination of the presence of the eggs of intestinal parasites for if present they may be contributing to production or maintenance of the deficiency

Coproporphyrin may be found in excess in the urine of pellagrins particularly those of alcoholic etiology involving liver damage according to Dobriner (1937)

PATHOLOGY

The earlier writers in describing the morbid anatomy of pellagra did not realize that they were dealing with a multiple deficiency disease and so included more than would present day writers The symptom complex has been broken down with the discovery of other members of the B complex and the realization of signs and symptoms resulting from the deficiency of these other factors in the diet However the close association of these factors in the various foods makes it seem very likely that the appearance of the signs of deficiency of any one factor augurs a subclinical deficiency of the other factors The treating of an isolated deficiency with the specific crystalline

vitamins may be followed by the appearance of signs of deficiency of one or more of the other factors It is now thought that most of the changes in the nervous system are due to thiamine deficiency A description of the pathology of niacin deficiency will be limited to lesions of the skin and gastrointestinal tract

In pellagrous patients Moore (1942) found pathologic changes both in the skin affected with characteristic lesions and in apparently normal skin from another part of the body These changes consisted mainly of dyskeratosis atrophy of the epidermis and inflammation of the cutis He thought the process was reversible because of a favorable response to treatment with niacin (nicotinic acid) The similarity of the microscopic appearance of pellagrous lesions to chronic inflammation of the skin makes it difficult to differentiate them The conditions with which the pellagrous lesions may be confused are eczema neurodermatitis and erythema multiforme It seems evident that the lesions of the skin are quite nonspecific in their appearance microscopically The explanation of the causation of the dermatitis is not known There is apparently some condition of the skin which makes it more susceptible to the action of irritative agents than normal skin At one time it was thought there was an increase in porphyrin in pellagra and from what was known of the sensitivity of the skin to sunlight in porphyria it was considered that a logical explanation had been found However it was difficult to explain the presence of lesions on parts shielded from the sun and those on patients who had not been exposed to sunlight Then it was demonstrated there was no increase in porphyrin in most cases of pellagra and that theory had to be abandoned

Sydenstricker (1941) reported that autopsies of patients dying of pellagra revealed fatty livers Microscopic examination showed extreme fatty degeneration He reported that one of these livers was properly prepared and used in treatment of a pernicious anemia case with the characteristic reticulocyte response However this liver extract administered to pellagra patients was entirely ineffective

The gastrointestinal tract generally shows atrophy and thinning of the mucosa In some portions there may be hyperemia which may progress to ulceration particularly in the terminal portion of the small intestine and the colon

It is probable that the changes in the epithelium are responsible for the diarrhea and have an adverse effect on the absorption of the nutrients Undoubtedly the far advanced cases reach an irreversible point beyond which it is impossible to absorb nutrients and it becomes necessary to provide them by parenteral injection if a recovery is to be effected The achlorhydria may arise as the result of the atrophy of the gastric mucosa and with adequate therapy the return of the hydrochloric acid to the stomach contents may be expected In the cases with diarrhea there may develop a sprue like syndrome which may be associated with a macrocytic hyperchromic anemia which has

recently been shown to respond to folic acid in adequate dosage This is probably just another indication of the marked multiplicity of deficiencies which, when combined, constitute the pellagra syndrome

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CHAPTER 63

COSMOPOLITAN DISEASES AS SEEN IN THE TROPICS

ANTHONY DONOVAN

GENERAL CONSIDERATIONS

Prior to World War II a common misconception among medical men practicing in temperate climates was that medical practice in tropical zones differed greatly from that of colder regions both in the incidence of the various diseases and in the clinical characteristics of human illnesses. The increased knowledge of actual conditions in the Tropics accumulating during the past few decades and especially the personal tropical experience during World War II of thousands of physicians formerly acquainted solely with temperate climates have effectively eliminated most of these erroneous concepts so that today there is a more realistic approach to the problem of disease as encountered in the Tropics and there is coming into being a body of scientific data and of trustworthy statistics which is dispelling the old hazy impressions and myths regarding tropical medicine.

The incidence of the various diseases in any part of the world depends on 3 general factors which in order of importance are (1) economic conditions (2) climate and (3) race. These 3 conditioning factors are usually inextricably interwoven. In any given area one or another of the 3 may play the predominating part in determining which of the illnesses of mankind are of most frequent occurrence but in general and especially as regards tropical countries it can be safely said that the relative order of importance of the 3 is as stated. Economic conditions and climate are especially closely related. It is not the purpose of this chapter however to discuss the relationships of climate economics and race to disease incidence other sections of this book are devoted to those matters and here the subject matter will be limited to pointing out some of the peculiarities in the natural history of the important cosmopolitan diseases—ailments of world wide incidence—as they occur in tropical regions.

TUBERCULOSIS

Faust (1944) states that with few exceptions all the cosmopolitan diseases are relatively prevalent in warm climates. Of these cosmopolitan diseases (which by definition excludes malaria) the chief scourge of the Tropics is tuberculosis. In most mortality tables from the hot countries tuberculosis usually ranks with or outranks malaria as the chief cause of death. For example the annual report for 1942 of the Health Officer of Panama City, Republic of Panama lists the 6 principal causes of death in the order named as tuberculosis pneumonia heart disease diarrhea and enteritis cancer and

nephritis For the city of Colon on the Atlantic end of the Panama Canal the health officer report of mortality rates for the same year lists as principal causes of deaths tuberculosis organic heart diseases pneumonias nephritis apoplexy and cancer (See Tables XXVII XXVIII and XXIX at the end of this chapter for the 5 year death rates (1938 1942) of the Panama Canal Zone Panama City and Colon) And of 13 729 autopsies performed at the Board of Health Laboratory Ancon Canal Zone from 1904 to 1942 tuberculosis leads the list as the most frequent cause of death 1 655 cases of tuberculosis *causing death having* been found in 13 729 autopsies (Report of Health Department of the Panama Canal 1942)

Tuberculosis is world wide in extent but tropical areas have much more of the disease than colder climates The role of the triumvirate of factors previously mentioned—economic conditions climate and race—will not be discussed here except to state the rather obvious conclusion that poverty and ignorance with attendant overcrowding poor sanitation malnutrition high birth rates and generally chaotic family life appear to be the contributing causes of a high tuberculosis mortality in the Tropics Mumford and Mohr (1944) in a study of the distribution of disease vectors and diseases on tropical Pacific islands *found that of 87 diseases occurring on 20 islands only* tuberculosis and influenza were found on all A perusal of the recent book *Global Epidemiology* by Simmons et al (1944) throws into sharp relief the predominance of tuberculosis as the principal cause or one of the principal causes of death *in all of the tropical countries* included in the volume The annual tuberculosis death rate per 100 000 population in the United States is now under 40 In many coastal cities of South America the death rates from tuberculosis approach 10 times that figure Bueno (1946) states that the tuberculosis death rate for all of Brazil is 250 per 100 000 population but that the coastal city of Recife capital of the State of Pernambuco has a mortality rate of 400 Callao port for Lima the capital of Peru has a tuberculosis mortality rate of 400 or over *and Guayaquil Ecuador approaches* 500 according to some reports Faust (1944) states that in India in 1938 the death rate from pulmonary tuberculosis was 2?3 per 100 000 in the United States in that same year the rate was 44 6

Clinical forms of tuberculosis appear to differ in no essential particular *in tropical areas as compared with temperate zones* There is a difference however in the incidence of the various clinical forms In newly opened tropical or subtropical regions where there is an indigenous population only recently exposed to outside contacts *there is often the development of massive* tuberculinization of the population with a high incidence of primary type of infection Records from Peru indicate that this occurred in the highlands of the southern part of the country deep inland in the Cuzco area following the construction of the Mollendo Arequipa Cuzco railway in the latter part of the nineteenth century and the first decade of the present one Bueno describes a similar picture in Brazil where the interior of much of the country is still in a stage of pre tuberculinization (in the capitals of the States of

Piauhy and Matto Grosso the tuberculosis mortality rates are 70 per 100 000 population) in contrast the heavily populated coastal area has a high incidence (in Recife capital and principal port of the State of Pernambuco the tuberculosis mortality rate as previously mentioned is 400 per 100 000) while in the southern part of Brazil where the general living standard is higher and where contact with the outside world has perhaps been more intense over a longer period of time than further north on the coast or than in the hinterland tuberculosis rates are dropping Tuberculous meningitis miliary tuberculosis gastrointestinal bone and joint infection with Koch s bacillus are all more frequent in tropical and subtropical regions than in temperate zones due primarily to poor sanitary conditions and to lowered resistance on the part of the individual as well as to inherent racial susceptibility

In general therefore it can safely be stated that tuberculosis is the principal cause of death in most tropical areas that it occurs in acute virulent forms less commonly seen in temperate zones and that its high incidence depends on the variable factors of economic conditions racial make up of the population concerned *climate to some extent and the immunologic status of* the exposed populations

THE PNEUMONIAS

Lobar pneumonia and bronchopneumonia are important causes of death in the tropics Bronchopneumonia is especially common in children under 10 years In tropical highlands pneumonia is probably the chief cause of death This is due to the poor state of nutrition of the general population the lack of adequate clothing and housing and the sharp changes in temperature and humidity which are common in the altitudes as for example in the Andes chain Clinically the disease seems to be most virulent among individuals who dwell at or near sea level and contract pneumonia when journeying at high altitudes and conversely it is said that people accustomed to the rarefied atmosphere of high altitudes show a high mortality from pneumonia when they contract the disease in the lowlands There is little statistical proof of these latter statements Additional factors in high pneumonia mortality in the Tropics are the usual ones of poor or nonexistent medical and nursing care lack of hospital facilities and deficient treatment especially the lack of availability of the newer antibiotics and sulfonamides There are however no important clinical differences in bronchopneumonia or lobar pneumonia in tropical as compared with temperate climates Applebaum and Shrager (1945) in a study of 500 consecutive cases of pneumonia at Gorgas Hospital in the Panama Canal Zone discuss the epidemiology of the disease and the reasons for higher incidence among certain racial and social groups and state that in general social conditions racial status and occupational environment seem to be more important than climate and it may be emphatically stated that pneumonia is not only a disease of temperate zones but merits equal attention under all climatic conditions

THE COMMON CONTAGIOUS DISEASES

Diphtheria

Diphtheria is definitely less common in the Tropics than in cold climates except that in urban communities in the temperate zones where there is a high level of public health practice the disease has almost reached the vanishing point However cities in mountainous regions in countries commonly considered as tropical *often show high incidences of diphtheria For example* the seaport and chief city of Ecuador Guayaquil with a hot humid climate has at least 10 times less diphtheria than the capital of the country Quito which although only a few miles from the equator lies at an elevation of about 9 000 feet and has an average year round temperature of about 52° F Recent rather serious epidemics of diphtheria have occurred in Buenos Aires Argentina and in Montevideo Uruguay cities with a temperate climate but with sanitary and public health facilities somewhat less developed than in comparable North American cities The disease appears to have the same general characteristics and clinical course in any climate (Pan American Sanitary Bureau 1931)

Whooping Cough

Pertussis tos ferina or whooping cough is prevalent in tropical climates but again as with diphtheria incidence and fatality rates are higher in the *tropical highlands In the Andes chain in South America frequent epidemics* range through the Indian populations and whooping cough is one of the chief causes of death in children under 2 years of age in these regions Again there are no important clinical differences in the disease as encountered in tropical lowlands tropical highlands or temperate zones which are not explainable on the bases of racial characteristics general nutritive and *physical status of* the populace and availability of competent medical attention

Scarlet Fever

As with streptococcal infections in general scarlet fever is relatively rare in the Tropics In 2 132 autopsies performed on children 10 years of age and under reported by Kean from the Isthmus of Panama (1946) only 4 deaths *were attributed to scarlet fever Sporadic cases occur almost anywhere in* tropical or subtropical climates but there are few if any reports of epidemic outbreaks of the disease in torrid zones When cases do occur they are usually mild at least in recent years This appears to coincide with the general mildness of the disease as reported from the United States in the past 5 years The disease *does not present an important problem to the practitioner in the* Tropics

Smallpox

Almost though not quite eliminated from temperate climes smallpox or variola is still an important medical and public health problem in *tropical* countries Much has been accomplished in the past 25 years in the way of vaccinating the general population in most countries of the torrid zone *but still*

sporadic outbreaks occur even in the cities One factor to be kept in mind in organizing vaccination programs in hot climates is the necessity for careful refrigeration of the vaccine otherwise much of the work done will be wasted effort and a false sense of security will be engendered Often the responsibility of vaccinating masses of people is left to poorly trained and poorly controlled nonmedical personnel who are not instructed in the need for careful preservation of the vaccine In recent years and especially in Venezuela a mild form of smallpox called *alastrim* has frequently been reported mortality is almost nil and it has been said that any fatalities in an outbreak of supposed alastrim should cast doubt on the diagnosis Clinically smallpox presents the same characteristics whether seen in temperate zones or in the Tropics

Measles and German Measles

Measles and German measles especially the former are relatively common in the Tropics and appear to present similar clinical characteristics in any climate Measles is frequently fatal in tropical zones due to secondary bronchopneumonia otitis media and other complications

Mumps

There is little that need be said here about mumps It occurs in the Tropics with about the same frequency as in temperate climates and has no distinctive clinical characteristics in hot countries as compared with temperate and cold lands

Chicken Pox

Chicken pox is common in all parts of the world is hardly ever fatal appears to have uniform clinical findings wherever it occurs and warrants no further discussion in this place

Meningitis

There appear to be decided differences in the incidence of the meningitides in different latitudes especially when the various causative agents are considered Kean and Crandall (1944) in a study of meningitis on the Isthmus of Panama noted a higher incidence of pneumococcic meningitis in the hot cities of Panama (22 9 per cent of all meningitis cases) and New Orleans (23 7 per cent of meningitis cases) than in New York City (8 4 per cent) or Chicago (15 5 per cent) They stated that the incidence of tuberculous meningitis is high and that of meningococcic meningitis is low in Panama whereas streptococcic meningitis seems to occur about as frequently in Panama as in cities of the United States It was further stated that streptococcic infections in general (puerperal sepsis septic sore throat, scarlet fever rheumatic fever) have a lower morbidity and mortality rate on the Isthmus of Panama than in the United States but that the occurrence of streptococcic meningitis is about equal in the 2 areas

During recent years severe epidemics of meningococcic meningitis have raged in Chile especially in the cities of Santiago and Valparaiso but these localities are of course not at all tropical in climate or situation

In general it can safely be stated that meningococcic meningitis is infrequent in the Tropics that tuberculous meningitis is more common than in temperate climates that pneumococcic meningitis is also more often seen in tropical areas and that the other forms of meningitis occur with about the same frequency in the Tropics as in temperate zones No marked clinical differences are seen in any latitude

Poliomyelitis

Poliomyelitis a disease of the central nervous system about which there is much that is still obscure especially regarding epidemiology and transmission is apparently less common among the poorly nourished ill clad debilitated masses existing in many tropical areas than among the well fed well cared for residents of the temperate zones of the earth In fact there is statistical evidence indicating that the higher the economic and social level of a population the more frequent is the occurrence of poliomyelitis No attempt will be made here to go into the possible reasons for this It is true that cases of the disease are seen sporadically in the Tropics and also that poliomyelitis appears to be on the increase in tropical and subtropical countries (viz recent outbreaks in Colombia and in Costa Rica) This may possibly be paralleling the general advance in economic and social well being and the increased contact with the outside world that is taking place in most tropical countries No further discussion seems warranted here since so much awaits further elucidation by more intensive research into the natural history of the disease

CARDIOVASCULAR RENAL DISEASES

Rheumatic Fever

Until recent years most authorities have stated that rheumatic fever is uncommon in the Tropics Opinion is now changing and it is recognized that the disease is not at all rare in the torrid zones There is evidence to indicate that this is due to an actual increase in the incidence of the disease and not to mistaken diagnoses on the part of practitioners in former years Hardgrove Whittier and Smith (1946) reporting from the Gorgas Hospital in the Panama Canal Zone found a decided increase in the number of cases since about 1927 and stated that there were no tenable explanations for the increase in the incidence of the disease Levine (1946) stated that rheumatic heart disease was uncommon but not rare among the natives of eastern New Guinea and expressed the opinion that the more carefully people in the Tropics are studied the more rheumatic heart disease will be found The reports from the National Institute of Cardiology of Mexico (Chavez et al) are worthy of study in this connection Mumford and Mohr (1944) found

rheumatic disorders to be relatively common in their survey of 20 tropical Pacific islands There appear to be no significant clinical differences in the disease as seen in the Tropics and in temperate zones

Hypertension and Hypertensive Cardiovascular Disease

There is a paucity of comparative data concerning the incidence of hyper tensive cardiovascular disease in the Tropics as compared with temperate zones In general, there seems to be little doubt that the relative occurrence of high blood pressure, generalized arteriosclerosis, arteriosclerotic heart disease, cerebrovascular "accidents" and coronary artery disease is considerably less in the Tropics than elsewhere It also appears evident that there are marked racial differences in susceptibility to the hypertensive diseases Kean (1944) took the arterial blood pressures of a primitive Indian group in the Panamanian Tropics and found an average reading of 105 2 systolic and 69 3 diastolic (in 407 Indians of the San Blas Archipelago), with no hyper tension in any individual In a study of the racial distribution of nephritis and hypertension in Panama Taylor (1945) encountered hypertension (with diastolic pressure over 100 mm Hg) to be 6 times more common in West Indian Negroes than in native Panamanians and 3 times as common in the Negro group as in whites He also reported arteriolar nephrosclerosis to be 7 times more frequent in the West Indian Negroes than among Panamanians and 3 times as frequent among the former as in the white race Glomerulonephritis was rare and mild, pyelonephritis being more frequently seen

Calculi in the Urinary Tract

Davalos (1945) states that the world's chief "stone areas" are India South China, Egypt, Mesopotamia and Holland Renal and ureteral calculi are common in the southern part of South America especially in north and central Chile, and in Argentina In Brazil there are many cases in the north east and in the south but the disease is rare in the Amazon basin Davalos examined 60,000 persons in a humid hot region of southern Ecuador without finding evidence of stone in a single individual Vermooten, discussing this paper, said that 1 case of renal calculus had been found in 1 million hospital admissions in South Africa Diet water supply and racial characteristics appear to influence the incidence of stone The region around Mérida, on the Yucatan peninsula of Mexico, is notorious for the high incidence of kidney stone, this is a limestone area with a high calcium content in the drinking water Rose (1945) found many cases of kidney stone in the tropical zones of Australia, which he attributed principally to insufficient fluid intake on the part of the residents of the area

OTHER COSMOPOLITAN DISEASES

There are very many other important diseases of world wide incidence occurring in the Tropics as well as in temperate climates, about which little can be said here authoritatively due to lack of trustworthy data Cancer and other

neoplasms are encountered everywhere in the world with apparently a higher incidence of certain types in temperate zones as compared with the Tropics and vice versa for example cancer of the stomach is probably more often encountered in temperate zone cities than in the torrid zones the same holds true for bronchogenic carcinoma whereas cancer of the skin is probably more frequent in the hot Tropics. Appendicitis is universal but there seems to be a lesser incidence among primitive peoples and also among races with unusual dietary habits. Diseases of the liver are common in tropical and temperate climates a higher incidence of liver abscess is certainly to be expected in areas with poor sanitary facilities where amebiasis is frequent but the comparative incidence of liver ailments such as the cirrhoses must await elucidation by many more autopsy reports from the Tropics. Mental illness and the psychiatric diseases are universal but again little can be said here as to their relative incidence in cold and hot countries. The venereal diseases are more frequent in the Tropics especially lymphogranuloma venereum and granuloma inguinale which are much less commonly seen in temperate climates as compared with gonorrhea and syphilis. Clinically there are no very remarkable differences in any of the above ailments as encountered in the Tropics as compared with the same disease entities in temperate lands. It is to be hoped that future work will enable more definite statements to be made regarding the world-wide incidence and the clinical and pathologic characteristics of the cosmopolitan diseases in tropical subtropical and temperate climates.

To conclude this chapter there follow 4 tables adapted from the 1942 Report of the Health Department of the Panama Canal (1942a) which are believed to be of interest and value in showing the principal causes of admission to hospitals and the principal causes of death in a carefully controlled tropical area. Disease and death in military personnel are not included in any of these tables. Table XXVI lists the diseases causing the greatest number of admissions of employees of the Panama Canal (white and Negro) to hospitals during the 5 years from 1938 to 1942 listed in order of frequency and giving the average incidence per 1 000 employees. During these 5 years the mean number of employees was 25 123.

TABLE XXVI DISEASES CAUSING GREATEST NUMBER OF ADMISSIONS TO HOSPITAL OF EMPLOYEES OF PANAMA CANAL 1938-1942

(Adapted from the 1942 Report of the Health Department of the Panama Canal)

DISEASE	AVERAGE RATE PER 1 000
Malaria	18.0
Diseases of nasal fossae and adnexa	10.6
Gonococcus infection	8.2
Pneumonias	8.0
Bronchitis	6.6
Diarrhea and enteritis	5.8
Hernia	5.8
Diseases of the heart	5.6
Diseases of the pharynx and tonsils	5.4
Syphilis	4.6
Appendicitis	4.0

Table XXVII which lists the principal causes of death from disease among the Canal Zone population for the 5 year period 1938 1942 is of special interest when compared with Tables XXVIII and XXIX which show respectively the principal causes of death from disease among the populations of Panama City Republic of Panama and of Colon Republic of Panama during the same 5 year period The differences in the death rates for specific diseases are highly instructive and reflect the effects of general hygiene economic status and racial background on mortality rates

TABLE XXVII PRINCIPAL CAUSES OF DEATH FROM DISEASE CANAL ZONE POPULATION 1938 1942

(Adapted from the 1942 Report of the Health Department of the Panama Canal)

DISEASE	AVERAGE RATE PER 1 000
Organic disease of the heart	0 868
Cancer	0 534
Nephritis	0 484
Pneumonia	0 410
Tuberculosis	0 328
Syphilis	0 224
(Mean population 48 014)	

TABLE XXVIII PRINCIPAL CAUSES OF DEATH FROM DISEASE PANAMA CITY 1938 1942

(Adapted from the 1942 Report of the Health Department of the Panama Canal)

DISEASE	AVERAGE RATE PER 1 000
Tuberculosis	2 134
Pneumonia	1 3[illegible]6
Organic disease of the heart	0 9[illegible]8
Nephritis	0 730
Diarrhea and enteritis	0 718
Cancer	0 666
(Mean population 109 700)	

TABLE XXIX PRINCIPAL CAUSES OF DEATH FROM DISEASE COLÓN 1938 1942

(Adapted from the 1942 Report of the Health Department of the Panama Canal)

DISEASE	AVERAGE RATE PER 1 000
Tuberculosis	1 846
Pneumonia	1 434
Organic disease of the heart	1 380
Cancer	0 83
Nephritis	0 742
Apoplexy	0 680
(Mean population 43 659)	

It will be noted that tuberculosis was fifth in the list of causes of death from disease among the Canal Zone population with a mortality rate per 100 000 of 32 8 which compares favorably with the rates in the United States whereas in the Panamanian cities of Colon and Panama City tuberculosis was first on the list of causes of death and the mortality rate for Colon was 184 6 per 100 000 population and for Panama City which is said to be one of the most crowded cities on earth the tuberculosis death rate was 213 4 per 100 000 *

*Editor's note (O F) In 1939 in Java death caused by tropical diseases was only 5 per cent of the total deaths.

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*Additional useful information can be found in the Bulletin of the Pan American Sanitary Bureau (Boletin de la Oficina Sanitaria Panamericana) published monthly in Washington D C

CHAPTER 64

THERAPEUTICS OF TROPICAL DISEASES*

HECTOR J ROSSELLO

The therapeutics in tropical medicine is not simple or limited only to administration of specific medication against the cause It is necessary also to combat other possible associated infections, such as syphilis, tuberculosis, malaria, intestinal infections It is often necessary to improve the patient's diet, because of the frequency of avitaminosis, hypochromic anemia, and hypoproteinemia The excellent results obtained in Puerto Rico and in Brazil by a North American mission illustrated the fact that treatment of the anemia due to ancylostomiasis by enriching the diet so improves the condition in some cases that there is no need for specific anthelminthic therapy

The severity of tropical diseases usually results in physiopathologic syndromes which may take precedence in the clinical aspect of the disease For example severe diarrhea due to bacillary dysentery results in dehydration which must be specially treated Again the syndrome of hyperpyrexia seen in certain severe forms of malaria may require its own therapeutics Shock may also be the result of definite tropical parasitic or bacterial affections Summarizing therapeutics must include combating all serious general and local disorders

Another very important consideration is the frequent necessity of "mass treatment" in many tropical regions where the disease has spread to regions of general poverty Under such conditions the exigency of speed in technics of administration the necessity of "average dosage" adaptable to the average level of individual tolerance, and, finally, economic considerations, all may oblige the physician to use therapeutic procedures applicable to the common level which are entirely different from those needed in treatment of the individual patient

Summarizing, the therapeutics of so called "tropical diseases" may demand application of the following which should form a part of the physician's "must" medicinal formulary

1 Administration of *specific medicaments* capable of directly combating the cause of the disease, such as parasite, bacterium, toxin, by expelling, destroying or neutralizing it The administration of most of these agents often consists of repeated courses, carried out according to plan or program which may be reduced to a veritable "therapeutic scheme"

2 Administration of *symptomatic* and *general medicaments* to combat symptoms

3 *Treatment of associated infections* (microbic, parasitic) In tropical regions, association with other diseases, such as syphilis, tuberculosis, bacillary

*See also each chapter and Chapter 65 for additional facts on this subject.

dysentery, is very frequent The physician must simultaneously treat these conditions which tend to aggravate tropical diseases

4 *The diet must be corrected and improved* The diet is often defective in many tropical regions, leading to latent or manifest avitaminoses, chronic hypoproteinemia, and hypochromic anemia A diet rich in vitamins, proteins and iron greatly aids the treatment

TREATMENT OF TROPICAL BACTERIAL DISEASES

Treatment of Bubonic Plague

Treatment of bubonic plague is possible with streptomycin Other therapeutic means are

1 *Specific antiplague sera*—Results are incomplete and questionable

2 According to some authorities, *sulfonamides* are only slightly effective

3 *Other agents* which have been tried are Mercurochrome, acridine, injection of bacteriophage, diathermia, or even local fever therapy (Pasteurella does not reproduce at temperatures higher than 37° C)

Make an incision into the bubo, with drainage when the bubo is soft Early extirpation of the thickened gland, before it has softened, or cauterization *or destruction by chemical or thermal caustic measures, is contraindicated* because septicemia may follow

The following measures have been employed for general symptomatic purposes cardiac stimulants, morphine (an analgesic), saline purges blood transfusions, plasma therapy, etc The efficacy of any medication in bubonic plague depends *largely upon early administration*, since *death is almost inevitable after septicemia sets in* (90 to 100 per cent)

4 According to Sokhey, streptomycin is very effective in plague Aureomycin and Chloromycetin are being investigated

Treatment of Tularemia

Streptomycin is almost specific No other systemic therapy is necessary *Hot moist applications* over buboes are advised, with a weak antiseptic Incision of the bubo should not be carried out early, unless it has suppurated and is definitely softened In such cases, incision with simple drainage suffices Many authorities advise against it *For ulcerations, use hot moist applications* with a weak antiseptic For the dry ulcers, prolonged application of saturated *solution of magnesium sulfate is recommended* also applications of aqueous saturated solution of urea Conjunctival infection is treated with weak antiseptic irrigation, with applications of homatropine or semisaturated solution of magnesium sulfate (Foshay) For general symptoms fever, "typhoidal" state, the usual general symptomatic treatment is indicated Mild radiotherapy (x rays) has also been used effectively in bubonic forms Specific antiserum of Foshay, now commercially available, is used with variable results Sulfonamides, according to Curtis are successful to a certain extent, they are effective after the first week of the disease *Sulfathiazole is recom*

nended by Weilbaecher and Moss On the other hand, according to other uthors sulfonamides are of no benefit O'Hara has used neoarsphenamine uccessfully Chloromycetin and aureomycin are also indicated

Treatment of Leprosy

INTERNAL TREATMENT OF LEPROSY

The following drugs have been used dyes, as aniline derivatives, prin ipally methylene blue, substances of supposed chemotherapeutic action, as gold alts, organic mercurials, copper sulfate, organic arsenicals, antimonials sulfonamides, various iodine preparations, etc, vitamins, principally vitamins B_1 and B_2, human serum and plasma, heterogeneous sera, antidiphtheritic, antitetanic, antiophidic venom, so called antileprous sera, vaccines and specific antigens, also nonspecific antigens and vaccines—leprous antigens, tuberculous antigens etc diphtheria toxoid venom of snakes and other animals, vaccines of complex composition, and the sulfone drugs, as Promin Diasone, and Promizole

Promin—Very gratifying results have been reported by Faget (1947) in the treatment of leprosy by the sulfone drugs Promine, Diasone, and Promizole As a matter of fact, with but a few exceptions, only lepromatous leprosy and mostly far advanced cases were subjected to sulfone therapy All the lesions of leprosy respond more or less slowly to the therapeutic action of the sulfones

Promin is the sodium salt of p p' diaminodiphenylsulfone N,N' didextrose sulfonate Diasone is disodium formaldehyde sulfoxylate diaminodiphenyl sulfone Promizole is 4 2' diaminophenyl 5' thiazolesulfone Diaminodiphenyl sulfone, the parent chemical from which these drugs are derived, seems to be the active principle of each

The Promin treatment was initiated at the Carville Leprosarium in March 1941 by oral administration, but this proved to be too toxic and sub sequently intravenous injections were used in all cases The treatment is started with 1 Gm daily with gradual increase of the dose in an attempt to reach the optimal dose of 5 Gm daily In the majority of patients this dose was attained In some patients who develop repeated toxic reactions the maximum daily dose must not exceed 2 Gm Treatment should be discon tinued for 1 week, following each 2 weeks of daily intravenous injections of Promin The blood concentration of Promin following each intravenous ad ministration rises rapidly but is transitory The drug is rapidly eliminated in the urine and usually only a trace or none remains in the blood stream at the end of 24 hours In certain cases after a prolonged course of treatment Promin may accumulate reaching a level of 20 to 30 mg per cent after 24 hours In all such cases the dose probably should be reduced

The therapeutic effects are slow no definite improvement usually be coming manifest before 6 months of treatment Thereafter improvement is progressive with virtually no relapses No case gets worse under treatment After 6 months of treatment almost 25 per cent of the patients show some improvement After 1 year this percentage is increased to 60, after 2 years

dysentery, is very frequent The physician must simultaneously treat these conditions which tend to aggravate tropical diseases

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The following drugs have been used dyes as aniline derivatives principally methylene blue substances of supposed chemotherapeutic action as gold salts organic mercurials copper sulfate organic arsenicals antimonials sulfonamides various iodine preparations etc vitamins principally vitamins B_1 and B_2 human serum and plasma heterogeneous sera antidiphtheritic antitetanic antiophidic venom so called antileprous sera vaccines and specific antigens also nonspecific antigens and vaccines—leprous antigens tuberculous antigens etc diphtheria toxoid venom of snakes and other animals vaccines of complex composition and the sulfone drugs as Promin Diasone and Promizole

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to 75 after 3 years to almost 100 Clinical improvement is manifested by shrinking and flattening of small nodular lesions to complete absorption with only a pigmented spot remaining Larger and deeper nodular lesions disintegrate more slowly with subsequent scar formation Infiltrative plaques gradually subside with diminution of the inflammatory swelling and edema of the tissue Occasionally regrowth of hair may follow resolution of lepromatous lesions on eyebrows beard arms and legs Mucosal lesions are more responsive than cutaneous lesions Oral ulcerations heal within a few months to a year Nasal obstruction is relieved Epistaxis is checked Improvement in leprous laryngitis occurs frequently with restoration of the patient s voice and relief of dyspnea Emergency tracheotomies become unnecessary * There is occasional improvement of impaired vision

Another feature in improvement during sulfone therapy is the reversion of bacteriologically positive skin and nasal smears to negative This is in direct proportion to the duration of treatment During the first year practically all cases remain positive for bacilli During subsequent years of treatment an ever increasing proportion of patients revert from positive to negative in the routine monthly skin and nasal smears After 4 years of continuous intensive treatment the incidence of negative reports exceeds 50 per cent Promin appears to eliminate bacillary infection from the blood stream and the small vessels thereby preventing the formation of new lesions (Fite and Gemar 1946) The histopathologic changes which occur are predominantly of an atrophic nature with gradual lessening of the number of acid fast organisms present in the lesion to the point of final disappearance

At Carville Leprosarium Faget reports that 19 Promin treated patients have been discharged as disease arrested following 12 consecutive months of negative bacterioscopy Of this number 3 were under treatment for 1½ to 2 years 3 from 2 to years 6 from 3 to 4 years and 7 from 4 to 5 years He notes further that penicillin used in large doses in the treatment of leprosy proved unsuccessful Other antibiotics deserve further investigation as possible chemotherapeutic agents against leprosy

Diasone was used in leprosy by Faget Pogge and Johansen (1946) by mouth in daily doses varying for adults from 0 33 to 1 0 Gm and for children from 0 17 Gm to 0 5 Gm The drug has an advantage over the other sulfone drug just described Promin in that Diasone is well tolerated by mouth by most patients whereas Promin must be given intravenously because of its toxicity by mouth Faget Pogge and Johansen (1946) reported on 104 patients treated in the National Leprosarium for 2½ years Of these 66 had received treatment for 6 months or longer 74 2 per cent of these patients were predominantly lepromatous cases 20 4 per cent of frankly mixed type and only 5 4 per cent neutral In 30 per cent leprosy was far advanced in 51 per cent moderately advanced and in 19 per cent the lesions were minimal

* Editor s note (R. B H G) This is a striking advance The Editor recalls the numerous tracheotomies which he saw in the Leper Colony at Molokai some years ago procedures which became very necessary in many cases of laryngeal leprosy

At the time of writing the report in 24 per cent of these patients skin scrapings were bacteriologically negative There was objective improvement in the specific leprous lesion in 65 per cent of patients treated for 6 months and longer In 23 per cent the improvement was subjective and no demonstrable change was claimed There were no cases that were clinically worse

It would appear from this report that Diasone has an action similar to that of Promin Treatment with Diasone has the advantage already stated the drug is well tolerated by mouth in doses up to 1 0 Gm daily for long periods of time Hematuria occurred in some patients but after a system was inaugurated beginning with a small dose of 0 33 Gm daily for the first 2 weeks and then gradually increasing to 1 0 Gm no cases of hematuria occurred

Chaulmoogra Oil Esters and Salts—Chaulmoogra oil is a stable oil extracted by pressure or drainage by use of ether etc from seeds of certain trees of the genus Hydnocarpus (*Flacourtiaceae* origin British India) This produces the best oil There are also other species of Hydnocarpus found in other regions (*Hydnocarpus wightiana H anthelmintica* etc) These other species of trees are found in British India Burma Indo China South China the Malay Archipelago Central Africa etc In Brazil there are certain trees of the family Carpotroches the seeds of which are also rich in chaulmoogra oil

1 *Oral administration* is not as popular as it formerly was because it causes gastric disturbances Sodium salts are better tolerated orally the salts are commercially available in tablet form Ethyl esters are also administered in capsules

2 Administration by *intramuscular injection* is preferred at present diluted with olive oil with an analgesic as for example in the excellent formula of Mercado

Mercado Heiser Formula

Chaulmoogra oil	60 Gm
Olive oil	60 Gm
Resorcin	4 Gm

For intramuscular injection begin by giving 1 cc every 2 or 3 days increasing slowly to 6 or 8 cc every 2 or 3 days continuing over a long period of time

The intramuscular injection of ethyl ester a more fluid and volatile liquid than the oil diluted in equal parts of olive oil with an analgesic is preferable

E C C D Formula (Muir)

(Prepared by Smith Stanistreet Co Calcutta)

Ethyl ester of oil of chaulmoogra	1 cc
Camphor	1 Gm
Doubly distilled creosote	1 cc
Neutral olive oil	25 cc

For intramuscular injection begin by giving 0 5 cc twice a week increasing slowly to 5 cc interrupting treatment after 12 injections (several courses)

3 *Intravenous injections* demand care and proper asepsis to prevent thrombophlebitis This method of injection has the advantage of being well tolerated In institutions where chaulmoogra therapy is still employed, it is the preferred method because of the better preparations which are available

Harper's Formula

Chaulmoogra oil	10 parts
Ether	1 part
Iodine	1 in 1,000

For intravenous injection, 0 5 to 1 0 c c once a week for many months Many authors state that intravenous injections of chaulmoogra oil are well tolerated when the oil is neutralized Pereira injects 1 c c of oil twice a week, rarely 1 5 c c or 2 c c, giving a series of 8 injections with intervals of 15 days

Treatment should be continued for a long time with intervals of suspended treatment for 15 to 30 days In addition to various complications due to lack of tolerance locally (gastric, intramuscular pain, endophlebitis), general febrile reactions may occur (leprous reaction) with depression, neuralgia, and bacillemia, which may require temporary suspension of treatment

Local intradermal injection with chaulmoogra preparations, the Philippine "plancha" method, is of controversial value It consists of the intradermal injection *(the needle entering barely 2 or 3 mm into the skin) of small doses* 1 or 2 drops in each intradermal puncture, making several punctures at one session, *repeating 1 or 2 or 3 times a week, puncturing around the border of the* lesion 30 or 40 times The same area, then, is not reinjected until after an interval of 1 or 2 months This procedure may be combined with or used alternately with other administrative procedures

Other Medicinal Agents—Their number is legion, but none are comparable to sulfone therapy

LOCAL TREATMENT OF LEPROUS LESIONS

Local treatment is a popular procedure in the treatment of infiltrating (lepromatous) lesions It effects regression, though at times irregular and incomplete

There may be an immunization reaction (*Rogers, Padrock, etc*) due to reabsorption of the products of the leproma, however, the reactions are apt to be acute and dangerous (*fever, bacillemia, etc*) *For local treatment of the* lesions, various agents and many procedures have been used

Local applications of *carbonic snow for a few seconds (to prevent vesica*tion) are applied to about 5 to 10 different lepromas each time and repeated *every 3 or 4 weeks, since* each application, especially at the beginning, may be followed by slight febrile reactions (Wayson, 1913) Padrock associates this method with injections of gold salts

Cauterization of the lepromas, by thermic, electrical, or chemical agents (brushing with trichloracetic acid in 20 to 50 per cent solution), may be performed

GENERAL TREATMENT OF LEPROSY

In addition to treatment with drugs, considerable importance is attributed to hygienic and general treatment (fresh air, physical exercise) and to adequate diet, of sufficient nutritive value, high in proteins, rich in vitamins, with low starch and fat content, it is important to avoid foods that require difficult and prolonged digestion, to prevent gastric obstruction, deranged digestion, *or constipation (frequent administration* of laxatives *is required)* Vitamin B_1 is especially indicated Treatment of other possible diseases frequently associated with leprosy in the Tropics is important—syphilis, scabies, malaria, tuberculosis intestinal helminthiasis, amebic dysentery, etc

SYMPTOMATIC TREATMENT OF LEPROSY

During the course of the prolonged development of leprosy, there occur acute periods that are more or less dangerous, accompanied by extension and aggravation of lesions, with bacillemia etc Neuralgia, sometimes very intense, as well as "leprous reactions," may also appear These may persist for 2 or 3 weeks, with extension or aggravation of the lesions Treatment of the neuralgia requires analgesic medicaments (antipyrine, Novalgin, salicylates, etc) which are not always efficacious also epinephrine, ephedrine, sodium salicylate (intravenously), fluorescein, histamine (1 1,000 solution intradermally), rachianesthesia etc Most authors prefer vitamin B_1 and intravenous calcium salts Treatment of the leprous reactions consists principally of bed rest, light dietary regimen, repeated mild saline purgatives avoidance of light (patient is frequently sensitive to light) avoidance of starches and fats suspension of any prior medication injections of calcium gluconate or of fluorescein intravenously, sulfur baths, etc After the fever subsides examine the patient carefully to discover whether new lesions have appeared

Results of the complex therapeutics in leprosy have been poor in the past when chaulmoogra has been the only treatment Better results may be expected in the future with the sulfones Development of the disease is slow in 30 to 50 per cent or even 70 per cent of the cases, according to various statistics, but the patient is always exposed to a possible new outbreak, recessive or febrile Probably 50 per cent of the cases that are slow in development and clinically healed are bacteriologically positive But even when they are bacteriologically negative, this is no assurance of real cure (Sakurame, concerning recurrences 20 years after apparently complete clinical cure), bacilli have been seen in glands or viscera in apparently cured subjects at necropsy (Neuman, Lara, Plant, Unna, Jeanselme, etc) However, a negative clinical and bacteriologic result permits social freedom to the individual, but no direct statements of absolute cure can be made

The most recent discussion on the therapy of leprosy took place at the 1948 Fourth International Congresses on Tropical Medicine and Malaria at Washington, D C, May 10 to 19 1948 R G Cochrane (1948) particularly discussed the treatment of leprosy with Promin, Diasone, and Sulphotrone While admitting that the sulfone drugs are powerful remedies for advanced and

moderately advanced lepromatous leprosy, he showed from his experience in India, that early lepromatous cases have not responded to sulfone therapy as rapidly as they have to adequately administered hydnocarpus oil and its derivatives combined with intensive intradermal medication He recommends sulfone therapy for the more advanced lepromatous cases, for those cases which have relapsed or have not responded to hydnocarpus therapy, and for lepromatous cases among the European mixed, and Mongolian racial groups This is in contrast with the experience in the United States where chaulmoogra therapy has not been effective whereas sulfones have been very promising

Treatment of Brucellosis

The following have been tried

1 *Streptomycin* combined with sulfonamide drugs *aureomycin* and *Chloromycetin* have proved effective

2 *Specific immunizing sera,* prepared from goats (Foshay et al), horses cows etc injected intravenously or intramuscularly 2 or 3 times a week in dosage of 20 to 40 c c, have sometimes proved efficacious, especially when injected in the beginning of the disease Sera from convalescent subjects have also been injected in doses of 100 to 300 c c Sera from human subjects who have been hyperimmunized by repeated injections of antimelitensis vaccines have also been used In some cases this has given excellent results (Carpenter) Specific serum therapy has also been associated with sulfonamides (Flippin etc)

3 *Vaccines,* which even now are commonly employed without evident justification should be used with caution, due to their frequent toxicity Injections should be made intramuscularly once or twice a week in increasing not too high doses The beginning treatment should be preceded by gauging the sensitivity of the patient (intracutaneous test), using various antigens such as Brucellergen etc intradermal injection of which provokes local erythema at the end of 24 to 48 hours in sensitive subjects Vaccine therapy is contraindicated in acute cases or acute periods and should be used only in chronic cases in which it should generally prove efficient Culture filtrates have also been used (Brucellin of Huddleson, Johnson, and Bates, 1933, 1936, Melitine of Burnet, 1922, etc) These are given by intradermal injection of 0 1 c c for the intradermal sensitivity test, followed by progressive doses given intramuscularly

4 *Sulfonamides* have been administered, associated or not associated with serum therapy, antibiotics or with vaccine therapy All the known sulfonamides have been used and the results have not been in agreement According to Blumgart and Gilligan (1939), there were 92 per cent cures with only 20 per cent recurrences Good results were also reported by Welch and collaborators and by Richardson On the other hand, according to other authorities return of symptoms is extremely frequent Even after symptoms disappear it is possible to find Brucellae in the blood which should justify the possibility of recurrence (Bethoux et al , Long and Bliss, Wilson and Maier, 1940)

Treatment of Rickettsial Diseases

Specific therapy was attempted with serum from hyperimmunized rabbits and with sera from other immunized animals but to date has not proved suc cessful

Sulfonamides and penicillin have no beneficial effects on secondary infec tion Snyder and co workers (1944) have administered p amino benzoic acid in 20 cases in Egypt by oral route maintaining blood concentration between 0 01 and 0 02 Gm per 100 c c

Excellent results have been obtained with aureomycin and Chloro mycetin

Convalescent blood has not shortened the development of the disease but has lowered the temperature and improved the general state of the patient Injections of crystalloid solutions sodium chloride or glucose are not efficacious and may even prove dangerous by increasing the edema The bad effect of glucose or saline injections has been noted by various authors (Ong and Raffetho 1940 Topping et al 1943 Harrel et al 1944 and others) These are to be used only when combined with sufficient plasma therapy Combat the hypoproteinemia with amino acids and protein concentrates Hepatic lesions frequently constitute an indication for the use of plasma therapy and the administration of vitamins Headache at times very intense due to cerebral edema or to increased cerebrospinal fluid tension and visual disturbances such as edema of the optic nerve should be combated by lumbar puncture

Vaccines used to prevent endemic typhus have not been successful in man (Dyer 1943)

Treatment of Verruga Peruana (Bartonellosis)

In both forms the acute febrile and the chronic eruptive cutaneous treat ment consists of penicillin aureomycin or Chloromycetin

Treatment of Diarrheic and Dysenteric Bacterial Diseases

Acute diarrhea and dysenteriform conditions caused by various Shigellae and Salmonellae frequently become widespread with an epidemic character They are serious because of the very marked dehydration

1 *Intestinal disinfection*—at present by use of various antibiotics and sulfonamide drugs with other medicaments such as purgatives intestinal oxy gen therapy and others Chloromycetin and Glucomycin are most promising

2 *Replacement of fluids lost*—by saline and glucose injections to overcome dehydration by plasma therapy to combat or prevent shock which is associated with this severe dehydration

3 *Antitoxic medication*—with specific antisera when possible

In addition to these 3 means of treatment an adequate diet should be maintained one which is nutritive principally in proteins (liquid semi liquid soft with little residuum)

moderately advanced lepromatous leprosy he showed from his experience in India that early *lepromatous* cases have not responded to sulfone therapy as rapidly as they have to adequately administered hydnocarpus oil and its derivatives combined with intensive intradermal medication He recommends sulfone therapy for the more advanced lepromatous cases for those cases which have relapsed or have not *responded to hydnocarpus therapy and for* lepromatous cases among the European mixed and Mongolian racial groups This is in contrast with the experience in the United States where chaulmoogra therapy has not been effective whereas sulfones have been very promising

Treatment of Brucellosis

The following have been tried

1 *Streptomycin* combined with sulfonamide drugs *aureomycin* and *Chloromycetin* have proved effective

2 *Specific immunizing sera* prepared from goats (Foshay et al) horses cows etc injected intravenously or intramuscularly 2 or 3 times a week in dosage of 20 to 40 c c have sometimes proved efficacious especially when injected in the beginning of the disease Sera from convalescent subjects have also been injected in doses of 100 to 300 c c Sera from human subjects who have been hyperimmunized by repeated injections of antimelitensis vaccines have also been used In some cases this has given excellent results (Carpenter) Specific serum therapy has also been associated with sulfonamides (Flippin etc)

3 *Vaccines* which even now are commonly employed without evident justification should be used with caution due to their frequent toxicity Injections should be made intramuscularly once or twice a week in increasing not too high doses The beginning treatment should be preceded by gauging the sensitivity of the patient (intracutaneous test) using various antigens such as Brucellergen etc intradermal injection of which provokes local erythema at the end of 24 to 48 hours in sensitive subjects Vaccine therapy is contraindicated in acute cases or acute periods and should be used only in chronic cases in which it should generally prove efficient Culture filtrates have also been used (Brucellin of Huddleson Johnson and Bates 1933 1936, Melitine of Burnet 1922 etc) These are given by intradermal injection of 0 1 c c for the intradermal sensitivity test followed by progressive doses given intramuscularly

4 *Sulfonamides* have been administered associated or not associated with serum therapy antibiotics or with vaccine therapy All the known sulfonamides have been used and the results have not been in agreement According to Blumgart and Gilligan (1939) there were 92 per cent cures with only 20 per cent recurrences Good results were also reported by Welch and collaborators and by Richardson On the other hand according to other authorities return of symptoms is extremely frequent Even after symptoms disappear it is possible to find Brucellae in the blood which should justify the possibility of recurrence (Bethoux et al Long and Bliss Wilson and Maier 1940)

Treatment of Rickettsial Diseases

Specific therapy was attempted with serum from hyperimmunized rabbits and with sera from other immunized animals but to date has not proved successful

Sulfonamides and penicillin have no beneficial effects on secondary infection Snyder and co workers (1944) have administered p-amino benzoic acid in 20 cases in Egypt, by oral route, maintaining blood concentration between 0 01 and 0 02 Gm per 100 c c

Excellent results have been obtained with aureomycin and Chloromycetin

Convalescent blood has not shortened the development of the disease but has lowered the temperature and improved the general state of the patient Injections of crystalloid solutions, sodium chloride or glucose, are not efficacious and may even prove dangerous by increasing the edema The bad effect of glucose or saline injections has been noted by various authors (Ong and Raffetho, 1940, Topping et al, 1943, Harrel et al, 1944, and others) These are to be used only when combined with sufficient plasma therapy Combat the hypoproteinemia with amino acids and protein concentrates Hepatic lesions frequently constitute an indication for the use of plasma therapy and the administration of vitamins Headache at times very intense, due to cerebral edema or to increased cerebrospinal fluid tension, and visual disturbances, such as edema of the optic nerve should be combated by lumbar puncture

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Treatment of Diarrheic and Dysenteric Bacterial Diseases

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1 *Intestinal disinfection*—at present by use of various antibiotics and sulfonamide drugs, with other medicaments such as purgatives, intestinal oxygen therapy, and others Chloromycetin and Glucomycin are most promising

2 *Replacement of fluids lost*—by saline and glucose injections to overcome dehydration by plasma therapy to combat or prevent shock which is associated with this severe dehydration

3 *Antitoxic medication*—with specific antisera when possible

In addition to these 3 means of treatment, an adequate diet should be maintained, one which is nutritive, principally in proteins (liquid, semi liquid, soft, with little residuum)

Treatment of Cholera

The syndrome of dehydration following diarrhea is *important* *Therapeutics* consist of *rehydration* by glucose and saline injections to restore the chloride level preferably by intravenous injection to combating *acidosis* by alkalinizing injections and plasma therapy Sulfonamide drugs have been found effective as well as antibiotics See Chapter 28

Treatment of Shigellosis

There is a certain relationship between the symptomatic aspect and the bacterial etiology It is admitted in a general way that infection by *Shigella dysenteriae* is the most serious largely because of the exotoxin of this organism Preparation of a curative antitoxic serum has been possible only with *Shigella dysenteriae* which is the only exotoxigenic form

1 **Intestinal Antiseptics** —Various intestinal antiseptics heretofore used especially calomel have been replaced by sulfonamide derivatives preferably the slightly soluble forms, principally sulfathiazole sulfadiazine sulfaguanidine Sulfasuxidine phthalylsulfathiazole phthalylsulfacetamide (Concerning phthalylsulfanilamide and others see Chapter 29) It is necessary to administer *the drug in doses which will attain sufficient concentration in the* middle intestine and which at the same time will be but slightly absorbed *and which will not cause toxic accidents* *For this reason sulfonamides are* generally ineffective and the various slightly soluble derivatives are also not efficacious In the administration of sulfonamides, it is always necessary to begin with a *heavy initial dose* continuing with *smaller maintenance doses* every 4 hours with *abundant fluid intake* to prevent renal and bladder precipitation Nausea and vomiting may make ingestion difficult See Chapters 29 and 30 for dosage

Weak doses are ineffectual
forming a subject easily into a
is to be continued until frequen
mucus pus and blood from the stools until the stools become formed and are of a pasty consistency and until Shigellae disappear All this requires on the average approximately 3 to 10 days Sigmoidoscopy constitutes an even more exact means of evaluating cure

Large quantities of liquids should be given to maintain abundant diuresis more than *1 500 c c of urine per day with the object of preventing renal* precipitation of the drug This is important in dehydrated subjects in febrile patients and in hot *weather* Maintain alkalinity of the urine by daily administration of 10 to 20 Gm of sodium bicarbonate which also serves to prevent renal precipitation of the drug by dissolving it in the urine

Clinical cure generally occurs in 70 to 95 per cent of the cases according to the drug used Negative stool cultures result in 50 to 80 per cent of the cases Persistence of bacilli in the intestines transforms the patient into a symptomless carrier heavier dosage is then necessary continuously applied to destroy all organisms

The action of sulfonamides may be supplemented by the administration of astringents such as bismuth subcarbonate or kaolin Intestinal oxygen therapy with slow injection into the colon of 250 c c of oxygen using a soft tube repeated 3 to 6 times a day is useful in cases which tend to become chronic The administration of purgatives should generally be avoided Some authors use purgatives but only in the beginning of the disease if there is no great dehydration and if stools are not too frequent also providing no tenesmus is present (20 Gm magnesium sulfate) Rectal instillation and enemata or colonic irrigation with astringents or other medicaments should be avoided Opiates—laudanum tincture of opium morphine etc —are indicated when pain is very severe and when stools are very frequent

2 **Aureomycin** and **Chloromycetin** are very effective also **Glucomycin**

3 **Rehydration—Plasma Therapy** —Dehydration as a result of the diarrhea constitutes the most frequent complication of bacillary dysentery It also induces oliguria azotemia alkalosis and loss of Cl The administration of large quantities of liquids is most important In moderate cases not showing great dehydration or prostration or profuse diarrhea give the patient 2 500 to 3 000 c c of liquids per day In fulminating cases with abundant diarrhea great dehydration hyperpyrexia and marked diminution of diuresis maintain diuresis at more than 1 000 c c per day by repeatedly injecting intravenously saline solution containing 5 per cent of glucose If dehydration persists with a tendency to shock plasma therapy is indicated

4 **Antitoxic Treatment** —Antitoxic treatment consists principally of injection of 100 000 to 200 000 units of monovalent antitoxin Injections should be given early and should be repeated They are effective solely against toxins due to the Shiga type

5 **Dietary Regimen** —A diet rich in carbohydrates and proteins liquid or semiliquid with but little residue should be administered the regimen called R B T (rice bananas tea) enriched by sufficient protein (egg white whey) amino acids (hydrolyzed casein) and vitamins (B complex and C) Later boiled egg beef juice potatoes cream boiled ham soft cheese soft boiled meat honey purees etc may be added

Treatment of Salmonellosis

Refer to Chapters 29 and 30

There is need not only for treatment of generalized infections due to typhoid and other salmonellas (typhoid and paratyphoid fevers) but also for treatment of localized enteritis due to salmonellas

Treatment of Typhoid Fever —Treatment of typhoid fever schematically includes absolute rest in bed proper hygiene of the mouth and skin maintenance of daily diuresis at 1 000 c c minimum (up to 2 500 to 3 000 c c of liquids per day) controlled cooling of the patient with cold packs application of ice to the abdomen lukewarm and progressively cooled baths etc proper nutrition treatment of complications In ataxo adynamic forms transfusions may be efficient Shock medication by injection of pyretogenous agents by

heterogeneous vaccines etc may doubtless shorten the development of typhoid fever in some cases by provoking a transient algid state but it is open to several dangers such as cardiac failure

Streptomycin aureomycin Glucomycin and Chloromycetin are promising especially the latter 2 antibiotics

Treatment of Enteritis and Alimentary Intoxication Due to Salmonellae — 1 *Administration of a purgative preferably saline* However if intense diarrhea lasts several days the purgative may be useless or even objectionable

2 Absolute abstinence *from water or food if vomiting occurs at least* for 1 day

3 Injection of liquids to combat dehydration isotonic saline or glucose

4 *Replacement of chlorides when vomiting is profuse by intravenous injections* of 10 to 20 c c of a 10 to 20 per cent solution of sodium chloride in water repeated during the day if necessary

5 If dehydration has persisted *for several days and prostration is extreme* there may be insidious toxic shock which will require repeated plasma therapy with amino acids oxygen therapy suprarenal opotherapy etc

Salmonellas are much less sensitive to sulfonamides than are shigellas Results are generally unsatisfactory

Abstinence from food for 1 or 2 days administration of liquids (rehydration by isotonic saline and glucose injections) carbohydrates amino acids (hydrolyzed casein by ingestion or by intravenous injections) restoration of chlorides by injection (not excessive) which may serve to combat intestinal meteorism use of plasma therapy oxygen therapy vitamins suprarenal opotherapy etc Administration of sulfonamides gives less efficacious results than in shigelloses Identification of the etiologic organism must be made in all cases to indicate the proper sulfonamide

TREATMENT OF TROPICAL VIRUS DISEASES IN AMERICA

Treatment of Dengue

Treatment of dengue is symptomatic Combat the orbital and dorsolumbar pains with salicylates antipyretic analgesics (antipyrine acetyl salicylic acid Novalgin etc) combat or relieve the febrile symptoms with hydrotherapy moist cold packs etc combat dehydration with copious administration of liquids Frequently strong dorsal pains pains in the limbs joints and cephalic pain impede the patient s movements and must be relieved by opiates *Later during convalescence the patient is profoundly prostrated* asthenic weak requiring proper nutritious diet vitamins especially vitamin B and tonics

Treatment of Lymphogranuloma Venereum

Treatment by use of sulfonamides is now most frequently used The action is virostatic but not virocidal Refer to Chapter 22

Sulzberger and Baer (1943) state that by means of simple rest in bed and hot applications recent adenopathy may regress in equal proportion and time Sulfanilamide has also been combined with other medication (Prats, Bereovitz, Costello, and Cohen) According to Grace, sulfanilamide should be given in courses of 1 or 2 weeks in increasing doses with a 2 week interval of rest

Mild and recent cases should be treated for 4 weeks Other cases and anorectal cases require 6 months to a year Grace states that 80 per cent of the inguinal forms are cured in 3 to 6 weeks, the remainder more slowly, anorectal forms, in 9 to 79 weeks, in 39 per cent of the cases, the majority of the remaining cases show considerable improvement

At present many authors advise alternating the Frei antigen with sulfonamides (Prats, Cornbleet, Brandt, and Greenblatt)

Other treatments have been local diathermy local radiotherapy immuno transfusion, extirpation of nodules and glands surgical treatment by colostomy in stenosis Aureomycin is excellent Bacitracin and Neomycin are good

Treatment of Yellow Fever

Treatment of yellow fever is neither specific nor curative and blood serum of convalescent subjects is not efficacious Symptomatic treatment is given to combat hyperthermia and vomiting Purgatives are not indicated, constipation is treated with enemata Hypoglycemia has been treated by glucose injections, increase of guanidine in the blood has been treated by calcium gluconate injections and the hemorrhagic tendency with blood transfusions It is proper to follow the present medication for acute hepatitis carbohydrates protein therapy (amino acids) nucleotids insulin plasma therapy, calcium The rapid diminution of diuresis and of the chlorides in the urine and in the blood is more difficult to combat Vitamin B_1 is indicated

TREATMENT OF PROTOZOAN TROPICAL DISEASES IN AMERICA

Treatment of trypanosomal diseases is still in the experimental stage The following drugs have been tried organic trivalent arsenicals (arsphenamine etc) or the pentavalent forms (Pentamidine, Tryparsamide) organic antimonials (Fuadin), iodine oxyquinoline (Yatren), colloidal iodine, emetine, Germanin (Bayer 205), azo derivatives of the benzidine series Synthalin, Atabrine, sulfanilamide Mazza found Bayer 7602 (Ac), by intramuscular injection, and Bayer 9736 (As) by intravenous injection, efficacious Bayer 9736 (As) acts upon other trypanosomes and also experimentally upon *T cruzi* Mazza (1945) verified its curative effects in several cases, although other investigators had not confirmed this (Chagas, 1942) These substances are not entirely harmless None have produced negative xenodiagnosis

Synthalin is an artificial derivative of guanidine (decamethylene diguanidine dihydrochloride) which has the property of causing hypoglycemia (Frank, Nothman and Wagner 1926) but it is not free from danger (hepatic lesions) It also exerts therapeutic action on mice infected with trypanosomes

(Janeso 1935 Schern Artagaveytia and Allende 1935) This action cannot be attributed to the hypoglycemia since the chemical also is trypanosomicidal in vitro in a very dilute solution (Yorke and Lowri 1937) Consequently it must act directly This fact has given rise to preparations of various derivatives of guanidine and Synthalin especially to certain diamidines which exercise a marked trypanosomicidal action both in vitro and in vivo (in rats and rabbits infected with *T rhodesiense*) Ewing (1944) *prepared numerous* aromatic derivatives some of which have proved to be definitely trypano somicidal Among these is diamidine stilbene which has proved effective in animal infections with *T rhodesiense T equinum* and *Leishmania donovani* etc *but is not effective against T cruzi*

Treatment of Leishmaniasis

Treatment of leishmaniasis should be given early to prevent extension of the lesions and invasion of the mucosa where ulceration occurs *Local treatment* is effective in the single cutaneous lesions or oriental button *(Leishmania tropica)* Treatment consists of radiotherapy cauterization with carbonic snow or carbonic anhydrate applied for a few seconds interstitial injection of hypertonic solution of sodium chloride or of the trivalent antimonial salt Fuadin or of berberine sulfate or of phosphoric acid etc In multiple extensive lesions which have already invaded the mucosa such as occur in American leishmaniasis *these local treatments are not applicable and are not* effective It is necessary to institute *general treatment* by internal medication Trivalent or pentavalent organic arsenicals given by injection etc have been somewhat effective but the best medication to date is the repeated and prolonged administration of antimony salts *principally the trivalent organic* antimonials by intramuscular injections of Antimosan or preferably of Fuadin (or Neoantimosan) Recurrences are frequent after variable periods the antimonials are less efficacious in this mucocutaneous form than in visceral leishmaniasis or kala azar For this reason it is necessary to prolong the medication it should be continued even after the cutaneous lesions have apparently disappeared since mucosal lesions frequently appear after apparent cure of cutaneous lesions Recurrences are fatal when small mucosal lesions persist especially in the nasal fossa Recurrence in the mucosa may occur very late sometimes 10 years after cure of the cutaneous lesions (Mazza etc) For this reason South American clinicians have emphasized the advantages of periodic repetitions of the series of injections Papillomatous hypertrophic forms are usually very resistant to antimony Fuadin has also been found ineffective after many repeated injections Some authors have advised at this point the combination with potassium iodide used as we have *applied it in tertiary syphilis*

Tartar emetic or double tartrate of antimony and potassium or sodium is also effective Apparent action is rapid and the lesions may disappear after 10 or 15 injections repeat to avoid recurrences Treatment which is not prolonged beyond *simple cicatrization exposes the patient to recurrence* (Dutra and Silva) The emetic is less easily tolerated than trivalent organic

antimonials and leads to numerous accidents (brachial neuralgia nausea vomiting hypotension cough salivation) Pentavalent antimonials are les effective

Secondary infections should be treated by the general anti infectio measures local disinfection of ulcerative surfaces internal administratio of sulfanilamide or penicillin

Visceral leishmaniasis is more readily cured by antimonials any of th 3 groups of antimonial salts may be used especially the pentavalent (Stibosan Neostibosan) Diamidine stilbene has also been used intravenously It i efficacious but complications are frequent congestion of the face sweating vertigo lipothymia headache etc usually transient which may be combatec by adrenalin For this reason the last drug should be used only in case resistant to antimonials

Treatment of Malaria

At present the South American physician uses 2 antimalarial drugs qui nine and its salt and Atebrine or quinacrine the action of which is especiall schizonticidal by destruction of the young asexual forms of the malarial para site Action against the sexual forms is much less pronounced and may eve be lacking In addition other less important adjuvant drugs are used th action of which is not actually antiparasitic and in less degree than the above A gametocidal action has been attributed to Plasmochin and for this reaso it has been suggested that it be used as a supplementary and associated med ication for the other 2 drugs It is somewhat toxic it has not been includec in the U S Pharmacopoiea XIV nor has it been accepted by the Americar Medical Association in its formulary (N N R 1945) Newer drugs ar Paludrine (Chlorquanide) Chloroquin (Aralen) oxychloroquine (SN8 137) Sontochin (SN6 911) Camoquin (SN10 751) Pentaquine (SN13 276) and Isopentaquine (SN13 274)

It is conceded that an *immunity reaction* is produced in the malarial sub ject during the course of the infection a reaction which has much to do with attenuation of symptoms and the temporary and ultimate disappearance o plasmodia from the blood with progressive reduction of fever This seem to occur spontaneously even when the patient has received no treatment The importance given to the idea of the immunity reaction has led to th suggestion that advantage should be taken of this fact and that therapeu tic abstinence' be tried at least temporarily Refraining from medicatior would permit the production of several febrile paroxysms which if not im mediately subdued would result in greater development of the immunity it has been demonstrated that definite suppression of later recurrences i achieved more clearly and with less delay in those patients whose febrile paroxysms have been intense and repeated in the invasion period of malaria and in the initial stages especially when the disease is due to *Plasmodium falciparum*

On the other hand immunity and suppression of recurrence is less com plete in *P vivax* infections the initial attacks of which may be moderate an

short The problem of temporary therapeutic abstinence was *fully debated* by the International Commission on Malaria (1933 1937) and the therapeutic procedure was summarized as follows

The subject is not to be treated in the first febrile paroxysms permitting 2 3 or 4 *to occur before administering antimalarial drugs* (quinine quinacrine) This idea of abstinence has been vigorously opposed by many authors who state that it is not possible simply by observation of the symptomatic aspect of the first febrile effects of a malarial patient to foresee the *ultimate development of subsequent* paroxysms and that it is often impossible to determine solely by means of hematologic examination during the initial paroxysms whether the patient has a tertiary (benign) affection due to *P vivax* or a mixed *P vivax* and *P falciparum* (malignant) infection In these *mixed forms P falciparum* infection which is of slower development shows fewer organisms in the beginning of the febrile attacks and thus it remains hidden by the abundant *P vivax* which predominates in the circulation in the first febrile paroxysms this has led hematologists to believe that the form present was benign tertian malaria Also schizonts of malignant malaria are smaller and disappear from the blood more quickly because of their adhesive properties

It is admitted that temporary therapeutic abstinence involves risk for the patient and in general it is considered more advantageous to give treatment immediately after making the diagnosis In addition the physician rarely sees the patient before 1 or 2 febrile paroxysms have already taken place (except in military establishments) Medication should be initiated immediately with quinine salts or with quinacrine (Atabrine)

It is necessary to keep in mind in administering the treatment the different clinical forms which malaria may present and the various periods of development during which the physician may be called to intervene

Treatment of the *typical intermittent forms*, benign tertian or quartan consists in the immediate administration of quinine or quinacrine by oral route in convenient dose following this general plan administration at the beginning of a saline purgative which will promote biliary discharge in patients who usually *have a certain degree of hepatocolic*

Quinine, preferably its sulfate is generally sufficient to retard the febrile paroxysms Other quinine salts have no advantage over the sulfate and the sulfate can be obtained at a lower cost It should be taken with a large glass of water *The physician must look for possible evidence of poor tolerance* (gastric) and nervous sensitivity (deafness vertigo agitation amblyopia) For children the dose should be reduced Quinine is eliminated rapidly and does not accumulate so that it must be administered repeatedly to maintain its effectiveness Some authors consider blackwater fever a quinine hypersensitivity

Atabrine (quinacrine) per os accumulates in the body because of slow elimination and administration should not be continuous Children tolerate

quinacrine better than adults Treatment should be interrupted for a period of several days it is repeated again according to the same plan

Combining quinine with quinacrine is not recommended since both act in the same manner (schizonticidal) combination of quinine with Plasmochin or of quinacrine with Plasmochin has been advised as the ideal treatment but at present it is difficult and not altogether free from danger (cumulative toxicity) *Discontinuance of these drugs for several months and removal of* the patient from the endemic zone generally prevents relapse

Treatment of *initial malignant forms* (falciparum pernicious forms coma tose bilious algid typhoidal) calls for immediate and energetic measures Generally poor gastric tolerance and hepatic congestion make oral admin istration difficult so that it may be necessary to administer the quinine by intravenous injection This procedure is used only in severe and pernicious forms Aralen per os however gives excellent results

TREATMENT OF TROPICAL DISEASES CAUSED BY SPIROCHETES AND LEPTOSPIRAS

Treatment of Relapsing Fever

Treatment of relapsing fever consists essentially of intravenous injec tions of neoarsphenamine It may be repeated for several days but cure may be effected by a single injection The injection may be made immediately after the beginning of the paroxysm or during the first hours If the first injection is insufficient a second is to be given preferably at the beginning of the second febrile period Injections should not be given immediately be fore a paroxysm because severe reactions may result (chills intense hyper thermia paroxysm vomiting etc probably due to rapid mass destruction of numerous spirochetes with liberation of toxin—Herxheimer reaction) Neither is it wise to give the injection during the afebrile period since the drug will be eliminated before the spirochetes again invade the blood Injection of neoarsphenamine during the first hours of a paroxysm primarily results in the disappearance of the spirochetes from the blood—not immediately but after several hours—followed by disappearance of the fever which may at times be elevated in the beginning

In some cases arsenicals have only partial and limited effect due to un duly resistant infection caused probably by arsenic resistant spirochetes Other arsenicals which have also been used successfully are Mapharsen sulfarsphenamine pentavalent arsenicals by oral route (carbarsone Stovar sol) We consider them less effective Intramuscular injections of various preparations of bismuth may be used in arsenic resistant cases as well as sulfonamides (sulfathiazole etc) Cure obtained in this way leaves a *state of immunity* which may persist for 1 year or more Penicillin was tried by Heilman and Herrell (1943) after Mahoney had obtained good results with the drug in syphilis In experimental spirochetosis in mice Heilman and Herrell noted disappearance of spirochetes from the blood in 24 hours with very considerable decrease in mortality these results have been verified

these patients should be principally specific against the amebiasis carried out by some form of iodo oxyquinoline (chiniofon or Vioform or Diodoquin) and by a pentavalent arsenical orally (carbarsone acetarsone Treparsol) and in refractory cases by bismuth orally and other drugs (see below) The administration of emetine is unnecessary in these chronic cases in the absence of acute episodes (diarrheal exacerbation pain etc) without reappearance of trophozoites in the stools

3 **Treatment of Patients With Simple Non Dysenteriform Diarrhea**—Treatment should be the same as treatment of the dysenteric form After completion of treatment it is necessary to examine the feces several times at 1 month intervals for amebae

4 **Treatment of Acute Amebic Dysentery**—Specific direct treatment of amebiasis consists as in the foregoing case in successive medication first with emetine by injection then with an iodo oxyquinoline orally and finally with some pentavalent arsenical orally In some cases with intense pain tenesmus and dehydration an adjuvant may be necessary for the pain and to relieve the general symptoms—dehydration oliguria fever toxemia avitaminosis secondary bacterial infection—dependent upon existing circumstances

5 **Treatment of Chronic Intestinal Amebiasis**—Acute dysentery is treated with emetine followed by a soothing agent In this acute episode (dysentery colic tenesmus frequent bowel movements) treatment must consist in the alternate administration of an iodo oxyquinoline (chiniofon) and of an arsenical (carbarsone) repeated or not repeated in alternating series According to some authors (Sellards Fernandez Fidel Cruz and others) complete cure may be effected in more than ½ of the cases according to other authors there is not so high a favorable percentage It might then become necessary to combine other medications including bismuth rectal administration of chiniofon and others However in chronic amebiasis especially if there are chronic rectal and colonic lesions rectal injections of different drugs are usually not well tolerated Nor are purgatives well tolerated even though it is tempting to administer them to combat the frequent constipation observed in these subjects Purgatives may provoke another exacerbation with colic tenesmus frequent mucosanguineous discharges etc Consequently it is preferable to refrain from administering them If there is great need for combating constipation lubricant evacuants are preferable (mineral oil etc) (After the use of oils stools must be very carefully evaluated) Iodo oxyquinoline usually constitutes an excellent medication when constipation predominates since it has a certain evacuant action when administered orally over a longer period combined or not with rectal injections

When it is necessary to administer sedatives for pain and spasm in the very acute intercurrent episodes opiates are useful also adrenalin belladonna rectal enemata to be retained of various mucilaginous substances like gum gelatin agar hot fomentations to the abdomen

When rectosigmoidal ulcerations predominate with frequent exacerbations of tenesmus diarrhea and colic provoked by no matter what the cause at times insignificant

(so called "dysentery by reactivation"), emetine is useful repeated in a series with or without local rectal medication with astringents or antiseptics or various topical medications

When inflammation and local reaction of a tumor like aspect exists, generally in the ileocecal region (amebic granuloma of the colon) or in the rectosigmoid region (rectal polyposis, rectal stenosis) or in the appendix (chronic amebic appendicitis), etc, emetine repeated in a series every two months is capable of a surprising reduction of the tumor Surgical intervention (for a supposed diseased appendix or extirpation of the tumor) may be disastrous and, if it is decided upon should *always* be preceded by medication with emetine No operation should be performed on these subjects without first having treated them with emetine medication in series since the emetine by itself may effect the cure of such appendicular and rectal tumor like lesions (granulomata) and if not it results in better preparation of the tissues for surgery

Finally, another point in considering subjects with chronic amebiasis is the advantage of effecting 'periodic cure with emetine" in the absence of any acute phase (constipated subjects with amebic cysts in formed stools) According to some authors emetine is unnecessary in such cases and they reserve it only for treatment of acute phases (Craig and others) According to others, one should give, periodically, medication with emetine in a more moderate series for example, 0 40 to 0 50 Gm total per series, alternating with other medicaments The older clinicians share this opinion (Chauffard, Dopter, and others)

Chloroquine was recently found to be an excellent substitute for emetine

Other medicaments have been proposed for exceptional cases in which definite disappearance of the amebae has not been accomplished in spite of the treatment The following have been recommended by various authors

Bismuth subnitrate or *bismuth subcarbonate* orally in large dosage suspended in plenty of water (10 to 30 Gm per day divided into small individual doses) Even larger doses have been proposed but they might be harmful

Rectal administration of different medicaments generally avails but little

6 **Treatment of Hepatic Amebiasis**—This is the most frequent extraintestinal localization of amebiasis, its frequency has been reduced since the use of emetine (Vedders, Rogers 1912) According to Rogers, in the British Army in India for every 1 000 patients with intestinal amebiasis before 1906 there had been 2 5 hepatic abscesses after 1912 (introduction of emetine) there were only 0 52

Every patient with intestinal amebiasis is exposed to amebic invasion of the liver through the portal circulation Rogers calculated (1928) that 2 to 4 weeks may pass after the beginning of amebic dysentery before a true abscess is formed during which period the liver may appear sensitive and enlarged In this period emetine causes a rapid and total reduction in hepatomegaly and disappearance of fever and hepatic pain and may prevent abscess formation It is also possible that emetine causes re absorption of small hepatic abscesses according to some authors, even larger abscesses may disappear It is difficult to determine the exact moment of suppuration Gen

erally the appearance of marked leucocytosis sweating daily remittent fever localized pain etc indicate abscess formation requiring surgical drainage (puncture or incision) *

Even in conditions demanding operative treatment it is best to give a course of injections of emetine hydrochloride as it has been found that post operative convalescence is much more rapid when this drug has been administered (Craig) However it is necessary to note that emetine considerably depresses the heart causing death during anesthesia This presents a difficult problem before proceeding with an operation *the heart should be examined thoroughly* or a few days should pass with withholding of emetine

Today due to emetine surgical drainage treatment mortality is less *than 1 per cent Manson Bahr states that he has been able to cure hepatitis* with emetine alone in 28 per cent of the cases with emetine and puncture in 47 per cent and with emetine and surgical drainage in 25 per cent However *in spite of its apparent simplicity puncture and drainage is preferable* It is necessary always to examine the pus from the abscess for the presence of motile trophozoites if emetine has not previously been administered After *the hepatic abscess has been drained and healed it is necessary to treat the* pre existing intestinal amebiasis

In *pulmonary amebiasis* in which the usual manifestation is the pulmonary abscess emetine may also exert a curative action with or without surgical drainage After noting the weight of the patient with an examination of the expectorated bronchial pus its quantity and appearance and noting the fever if these symptoms do not improve after emetine medication *Manson* Bahr (see Chapter 4) advises surgical drainage

Treatment of Conditions Due to Intestinal Flagellates and Ciliates

The pathogenic action of intestinal flagellates has been much discussed According to some authors these flagellates are simple saprophytes or are merely associated with other parasites in cases of *diarrhea* etc *At any rate* the mere presence of one of these parasites in the stools does not prove its pathogenic character

Giardia Lamblia —Various drugs *have been used but their efficacy is* generally inconstant

Organic arsenicals are useful but often fail They are often instilled directly into the duodenum as carbarsone

Atabrine causes rapid disappearance of the parasite from stools in 90 per cent of the cases Chloroquine is also effective Acranil has proved effective in doses of *0 50 Gm 3 times a day for 4 or 5 days for adults and ½* of this dose for children

Trichomonas Hominis Chilomastix Mesnili —*Trichomonas hominis* and *Chilomastix mesnili are probably not pathogenic* although some authors state

*Editor s note (O F) D Antoni and Sodeman recently proved that children manifest a liver phase of amebiasis which yields to 10 tablets of Diodoquin t i d for 20 days

that these parasites may cause diarrhea and enterocolitis The same drugs have been used as in Giardia infection

Balantidium Coli—Treatment is (1) per os emetine iodo oxyquinoline (chiniofon Vioform) organic pentavalent arsenicals (carbarsone), various anthelminthics (thymol oil of chenopodium) insoluble bismuth salts, (2) by rectal instillation enemata with iodo oxyquinoline ipecac permanganate organic silver salts etc (3) by modification of the dietary regimen to change the reaction of the intestine to an acid state since the parasite thrives in an alkaline or neutral medium administration of acid milks lactic acid and hydrochloric acid with an absolute milk regimen to decrease alimentary residue

TREATMENT OF DISTURBANCES CAUSED BY THE PRESENCE OF LARGE PARASITES IN THE INTESTINES AND ADJACENT ORGANS

(Nematodes Cestodes, Trematodes)

General Treatment of Tropical Intestinal Parasitoses

Treatment along general lines consists of

1 Diagnosis of the species of the parasite

2 Examination of the general condition of the patient for anemia or malnutrition with hypoproteinemia often due to poor diet or hypovitaminosis In these cases we combine with the direct anthelminthic medication measures to improve the general nutrition and metabolism

3 Preliminary preparation of the patient before administration of anthelminthic drugs Some anthelminthics are usually well tolerated and slightly toxic, e g hexylresorcinol pyrethrin tetrachloroethylene and others Others e g carbon tetrachloride santonin and oil of chenopodium are toxic and require proper preparation of the patient before administration to avoid accidents

4 Preliminary administration of purgatives Before use of anthelminthics preferably give a saline purgative or castor oil* (inconvenient because of its late and inconstant effect) or calomel combined with lactose in wafers or tablets The purgative is generally given the night before the oral administration of the anthelminthic and is indicated in all cases in which a large amount of mucus on the intestinal wall prevents the anthelminthic from attacking the parasite For the same reason it is necessary to reduce the intake of food before giving medication When some of the other anthelminthics are used however such as oil of chenopodium preliminary prolonged fasting is not indicated

5 Administration of anthelminthics The anthelminthics of choice are varied See under proper headings

*Editor's note (O F) Most North American authors disapprove of the use of oily purgatives because of the danger of facilitating the absorption of the anthelminthic drugs

The drugs are administered in different manners some in one dose others *in fractional doses to increase tolerance*

The drugs may be given in capsules wafers in suspension in water, or the taste masked in jelly honey or milk for generally these agents have a disagreeable taste During treatment the patient should remain in bed (hori*zontally) until the first evacuation occurs* and take no food since nervous complications are frequent

6 Administration of a purgative following anthelminthic medication is generally necessary Some anthelminthics are in themselves slightly purga*tive or at least they do not inhibit bowel movements With these* the administration of a postpurgative may be omitted, for example oil of chenopodium etc With others however purgation is necessary because the drugs may inhibit bowel movement In addition prolonged retention of the drugs favors toxic *accidents due to reabsorption e g carbon tetrachloride, the ingestion* of which must be followed in 2 hours by a saline purgative At times the purgative is administered simultaneously with the anthelminthic as the classical example of combination of santonin and calomel in capsules

7 *After evacuation the stool is examined for parasites the scolex or head* in the case of the large taenias The feces must be examined for a time after medication has ceased to estimate the possible persistence of eggs for if present the medication must be repeated Treatment usually need not be repeated before a lapse of 1 or 2 months

8 It is important to remember carefully the contraindications of anthelminthics This requires a knowledge of the patient s history the condition of the liver and the kidneys cardiovascular function possible presence of gastrointestinal ulcers and last possible association of several parasites in the same patient so frequently observed in American tropics—amebiasis ascariasis frequently combined with giardiasis ancylostomiasis etc For example the treatment of ancylostomiasis is different when it is combined with ascariasis than otherwise This modifies the principles governing anthelminthic therapeutics

9 It is rarely necessary to carry out symptomatic treatment in cases of helminthiasis since generally elimination of all or most of the parasites results in cessation of abnormal symptoms and functional disorders In some cases it may be necessary to combat the painful anal pruritus *especially* nocturnal which is frequent in oxyuriasis At other times it may be a nervous or reflex gastrointestinal disorder as in children convulsions and insomnia due to the presence of the large taenias or vomiting due to Ascaris *Less often more serious disturbances occur* such as appendix reactions simulating appendicitis (due to Oxyuris and Ascaris) or intestinal obstruction due to masses of Ascaris which have been paralyzed by the medication a state of chloroform anesthesia etc These cases are exceptional but the physician should keep them in mind Allergy constitutes a troublesome factor when

symptoms do not subside immediately after evacuation of the parasite Allergy may recur upon reinfestation

10 Parasites at times invade the circulatory and visceral systems, especially the abdominal organs and others This requires not only intestinal medication, but also general and internal drugs, for instance in cases of Schistosoma or Fasciola infestations

Treatment of Large Cestode Infestation

To verify cure it is necessary to find the head of the parasite in the stools

Preparation of the Patient—The patient is kept on a liquid or semiliquid low residue diet for 2 days—milk soup purée fruit juices—followed by administration of a purgative the day before medication If evacuation does not occur a 200 cc soapsuds enema is administered Anthelminthic medication should be administered the following morning, the patient remaining in bed, fasting

Anthelminthic medication may be *carbon tetrachloride* Patient abstains from fats and alcohol for several days before and after treatment Carbon tetrachloride is contraindicated in cases with hepatic lesions, alcoholism tuberculosis mixed infection with Ascaris Evacuation of worms occurs in 90 per cent of the cases with cure after but one medication in 65 per cent

Tetrachloroethylene is administered in the same manner and dose It is more advantageous and much less toxic than carbon tetrachloride (Lamson Brown and Robbins 1932) These 2 drugs are preferred in tropical regions where male fern becomes readily inactivated

Male fern, the oleoresin of the rhizome is also used It is inactivated rapidly by desiccation The oleoresin a thick liquid with a very disagreeable taste, is administered in capsules or in an emulsion with gum and water The patient must abstain from alcohol and fats for several days It is convenient to combine male fern with the simultaneous administration of calomel Toxic complications are frequent when the drug is given in high doses—nausea icterus albuminuria vertigo convulsions cramps There is a narrow margin between the active and the toxic dose

Pomegranate bark boiled in water, 15 Gm for children, 40 Gm for adults, is taken while fasting

Pelletierine tannate the alkaloid of the pomegranate, is sometimes used, *but this drug must not be given to children or pregnant women* Toxic accidents are frequent Relative efficiency, 30 to 40 per cent cure, has been noted by Stitt (1929) and Schroeder

The following drugs although less efficacious are also used thymol, hexylresorcinol pyrethrin, kamala, kousso (Brayera)

Acranil in tablets of 0 10 Gm giving 0 6 Gm per day or less, according to age and also Atabrine, 0 8 Gm per day, have been found effective See also Chapter 42

Treatment of Hymenolepis Nana Infestation

Male fern has been used (see treatment of taeniasis) and preferably hexyl resorcinol especially in children (Faust 1938 see treatment of ancylostomiasis) oil of chenopodium has also been used successfully (Brumpt 1938) Recently Acranil and chloroquine have been recommended

Treatment of Enterobiasis

Refer to Chapter 37

Treatment consists of the administration of anthelminthics orally local (rectal and perianal) treatment to destroy parasites and eggs with ointments enemata irrigations cleanliness personal hygiene of the hands of the perianal region *to prevent autoreinfestation finally treatment of troublesome* complications and symptoms especially anal pruritus If the patient can be kept clean for 2 weeks and free from parasites reinfestation will be prevented For this reason treatment must be repeated Treatment should begin with a full bath (especially in dealing with unclean environments or unclean patients or children) with soap and water repeated daily and daily change of all clothing in contact with the patient

Anthelminthics used are

1 *Gentian violet* is excellent and preferred by many (Faust 1930 Wright and Brady) Poor gastrointestinal tolerance is frequent—colic diarrhea nausea vertigo *Administration after a purgative is not necessary Ninety to 95* per cent of the patients are cured See Chapter 37

2 *Thymol* preceded by a purgative Patient must abstain from alcohol

3 *Hexylresorcinol* Previous administration of simple evacuant enema then hexylresorcinol orally (1 Gm for adults for children 0 1 to 0 2 Gm for each five years of age to be taken in one dose) then at night administration of simple evacuant enema with warm water finally administration of enema to be retained—250 to 500 c c of 1 1 000 aqueous solution of hexylresorcinol (ST 37 undiluted) To be effective a high enema should be given in order to reach the cecum Treatment should be repeated weekly over a long period of time several weeks

4 The following medicaments have also been used carbon tetrachloride (Chopra et al used as in ancylostomiasis) santonica (semen contra) and santonin (in the same manner as in ascariasis) bismuth carbonate

Phenothiazine was introduced by Manson Bahr Numerous other workers confirmed his findings E Kuitunen Ekbaum treated 1 275 patients with total doses of 2 5 to 9 0 Gm of phenothiazine and obtained 92 per cent cures *In small children* doses of from 1 0 to 7 0 Gm gave an 80 2 per cent rate of cure Untoward results are severe anemia and rare toxic hepatitis

Lubisan (m n butoxy phenyl diethyl carbamate) given in 1 2 Gm doses to adults on each of 3 successive mornings during which period no breakfast was eaten until 3 hours after the drug was taken followed by an ad

ditional 3 day course after a rest of 4 days resulted in cure in 37 of 51 patients Children under 12 years received reduced doses No evidence of toxicity was noted

Acranil cleared 4 out of 4 cases of enterobiasis The evening preceding medication the patient fasts, and the following morning a single dose (10 mg per kilogram) of Acranil is given After 3 hours a saline purgative is given

Local treatment consists principally in the administration of high enemata with simple warm water or with various solutions soapy water, water with 1 1 000 thymol 1 1 000 solution of hexylresorcinol 30 per cent glycerinated water 10 per cent saline solution 1 1 000 alum methylene blue essence of turpentine in oil (this may be irritant) Enemata which should be given high and retained afford immediate relief of pruritus

Local antisepsis may also be carried out by ointments (1 10 salicylic acid in petroleum jelly and lanolin simple mercurial unguent) Suppositories (calomel) may also be used or sodium salicylate etc

Enemata or oral treatment alone do not cure enterobiasis It is necessary to combine both treatments repeated enemata and anthelminthics, with full individual hygiene (hands anal region clothing) without this combination autoreinfestation is inevitable The complete combined treatment should be repeated several times

Treatment of Ascariasis

The treatment of ascariasis when the number of parasites does not cause complications is relatively simple It consists in putting the patient on a light dietary regimen with the administration of an anthelminthic (santonin oil of chenopodium hexylresorcinol or thymol) and then a purgative which is indispensable because the Ascaris is generally not killed by drugs but is simply made dormant and momentarily inhibited These worms must be expelled with the aid of a purgative Previous administration of the purgative is not necessary

1 *Santonin* This is still considered by some authors as the most efficient however it is readily toxic and for this reason has generally been abandoned, and is now used much less than heretofore

2 *Oil of chenopodium* is the most efficacious agent according to the majority of authors It can expel 70 to 80 per cent of the parasites after only 1 administration 80 to 90 per cent with two administrations practically equivalent to clinical cure It is more effective than santonin, however it is toxic and for this reason some fear to use it Use of the drug must be preceded by a dietary regimen high in carbohydrates and proteins and low in fats and free from alcohol (to improve the condition of the liver) and by a saline purgative given the day before if there is constipation Prolonged fasting favors intoxication The drug is contraindicated in patients with hepatic or renal lesions or with organic heart disease or in those with gastro

intestinal ulcers where absorption could readily occur The drug is very efficient but its major inconvenience lies in the fact that the therapeutic dose borders upon the toxic dose

3 *Hexylresorcinol* is considered very advantageous because 90 to 100 per cent of the ascarids are expelled with only 1 dose (Lamson et al) and because it is not toxic to any great extent A preliminary purgative is not necessary The patient must be on a light diet the day before administration of the drug The drug is given in the morning while fasting and for several hours afterward no food should be taken Hexylresorcinol exerts a certain cathartic action and a purgative may be omitted It is convenient however to give a saline purgative several hours after the drug has been taken or preferably the following day to provoke evacuation of dead ascarids Food especially oils fats and alcohol should be prohibited for several hours after the drug has been taken

4 *Thymol* is well tolerated and not toxic to any extent but is less efficacious than the foregoing medicaments See Treatment of Ancylostomiasis

5 The *chlorinated hydrocarbons* (tetrachloride tetrachloroethylene chloroform) should not be used since they anesthesize the parasite without causing it to be expelled and if the ascarids are very numerous intestinal obstruction may result from the accumulated masses of parasites

In cases with simultaneous presence of ascarids and ancylostomas frequently seen in certain American tropical zones it is preferable to omit tetrachloride which is very efficient against the ancylostomas It should be preceded by the previous expulsion of ascarids by oil of chenopodium or hexylresorcinol unless simultaneous administration of oil of chenopodium and of carbon tetrachloride is carried out as has frequently happened in mass treatment of groups during sanitary campaigns in tropical America This facilitates the work of administration in these mass treatments (see Treatment of Ancylostomiasis)

Treatment of Ancylostomiasis

Expulsion of ancylostomas by means of anthelminthics is generally not sufficient to cause disappearance of the anemia and hypoproteinemia In some cases the anemia has been improved without anthelminthics solely by instituting proper diet that affords sufficient nutrition It is necessary to improve the diet and to administer iron as well as food rich in vitamins proteins and iron The influence of ancylostomas and individual tolerance vary in different regions due to these dietetic factors According to Smillie and Augustine 25 worms might not cause trouble and some individuals might have more than 100 worms In Argentina observers (Fulleborn et al Orias etc) have found great numbers of parasites at times more than 200 coexisting with a good general state of health and normal hemoglobin They have attributed this tolerance to the diet (meat) of the inhabitants of these regions The kind of diet (lack of nutritional factors iron and proteins) exerts a predominant influence on the anemia due to ancylostomiasis in tropical America According to Ramon Suarez in 1930 the diet of the Puerto Rican rural

inhabitant consisted chiefly of bread cooked rice beans coffee and a scanty amount of vegetables According to Rhoads et al of the Rockefeller Institute the consumption of meat milk and eggs was very low Anemia was frequent and intense in patients with ancylostomiasis

There is also a very frequent coinfestation of ancylostomas with other parasites (Ascaris Strongyloides amebic dysentery malaria) which aggravates the patient s condition and makes treatment more difficult

Treatment of ancylostomiasis should include

1 Improvement in diet and nutritional state with food rich in proteins and of good quality (meat eggs milk) with high protein concentration (casein cheese) with added amino acids in serious cases (hydrolyzed casein) and with vegetables rich in vitamins

2 Administration of iron to combat the anemia In the opinion of some authorities medication with iron should be a part of the therapeutic procedure in anthelminthic treatment (W Cruz Pena Chavarria and Rotter Gabaldon Rhoads et al Marval) The principal preparations of iron recommended are iron ammonium citrate ferrous sulfate anhydrous not in aqueous solution ferrous carbonate reduced iron ferrous lactate Organic preparations of iron (hemoglobin) do not offer any special advantages

All preparations of iron are more or less constipating making frequent administration of an evacuant necessary (cascara sagrada) When gastric achlorhydria is present hydrochloric acid should be added Blood transfusion is indicated as an initial measure in any rather intense form of hypochromic anemia

3 Anthelminthic medicaments most used and most efficient are carbon *tetrachloride* and *tetrachloroethylene* which is not as toxic The latter may be repeated for 2 or 3 days using the same prescription as for carbon tetrachloride For use of oil of chenopodium see Treatment of Ascariasis

When both ancylostomas and ascarids are present administration of halogenated hydrocarbons may be dangerous since it paralyzes the Ascaris causing intestinal obstruction It is necessary first to eliminate the ascarids before using carbon tetrachloride or as suggested in several mass treatments oil of chenopodium 1 c c may be mixed with carbon tetrachloride 2 c c and the mixture ingested at one time while fasting It is preferable to proceed carefully with each individual treatment

Finally health education sanitary regulations (sanitation of the soil) and individual hygiene are indispensable in preventing reinfestation

Treatment of Strongyloidiasis

Treatment of strongyloidiasis consists in administration of anthelminthics but this may prove difficult because of the undue resistance of the parasite, which is imbedded deeply in the sinus of the mucosa Carbon tetrachloride and oil of chenopodium are not effective Although Willis states that a cure (disappearance of the larvae) has been effected in 2 or 3 weeks in 80 per cent of patients by the weekly administration of 1 5 c c of oil of chenopodium this medicament is considered practically ineffective

Thymol much in use in former days generally is not successful

Hexylresorcinol is also given

Gentian violet is more efficient and is much used at present The greatest inconvenience is gastric irritation which may result in nausea vomiting and intestinal discomfort This drug is not always active (persistence of larvae in stools) and frequently the treatment must be repeated See Chapter 37

Treatment of Trichuriasis

Treatment of trichuriasis consists in the administration of various anthelminthics which frequently fail to effect a cure hexylresorcinol (fairly effective) pentavalent arsenicals per os (very efficient according to some authorities) gentian violet finally also ficin *leche de higueron* which seems to be the most efficacious medicament (60 c c for adults or children) This is given in the morning while fasting A saline purgative or a high enema is indicated the night before It is not necessary to administer a purge after treatment This drug is considered capable of effecting cure in 85 to 90 per cent of all cases It is nontoxic and may be repeated without danger but is difficult to obtain

TREATMENT DIRECTED AGAINST NEMATODES AND TREMATODES WHICH INVADE THE CIRCULATORY SYSTEM AND THE VISCERA

Treatment of Filariasis

No specific medicament is known Many drugs have been injected into the veins to destroy the parasite but it is generally quite difficult to reach them in blocked lymphatic areas Antimony salts have been used in the same manner as against schistosomas and with frequent but not constant success tartar emetic intravenously (Rogers 1917 later Macfie 1920 Muhlens 1921 Roy and Bose 1922 Diamantis 1923 etc) trivalent organic antimonial salts principally Fuadin (Peter 1926 Shewar 1932 Paterson 1932 Fischer 1933 Bruce 1933 etc) Anthiomaline or thiomalate of lithium and antimony (2 to 4 c c of 6 per cent aqueous solution by intramuscular injection on alternate days 10 injections)

Of a number of trivalent and pentavalent antimony compounds studied extensively by several groups of investigators Neostibosan (diethylamino p aminophenyl stibinate) proved to be the most effective A permanent micro filaria reduction of 91 to 99 per cent was observed in 35 patients It is not known if the adult worms die or are sterilized by action of the drug In 75 per cent of the patients all circulating microfilariae are eliminated

Thetford Otto Brown and Maren used Arsenamide in 18 cases observing a microfilariae reduction of 99 per cent and a permanent elimination in 72 per cent Only minor toxic reactions occurred

Another chemotherapeutic agent Hetrazan (1 diethylcarbamyl 4 methyl piperazine hydrochloride) developed by Lederle was administered orally to

74 patients Of the 26 cases which were under observation for a year a 99 per cent reduction in circulating microfilariae was noted while 54 per cent became permanently negative Although a number of patients experienced mild toxic manifestations at no time was it sufficiently severe to necessitate discontinuation of therapy

H Galliard of l Institut de Parasitologie Paris France observes that radiation is helpful in the chyluric type of filariasis

Treatment of secondary infection is local (sulfanilamide local hot applications heat) and general (sulfanilamide penicillin various vaccines) Treatment of lymphatic obstruction is only palliative (rest in bed elevation of limbs permanent compresses or elastic bandages) Diet should be low in fats Small incisions or punctures of the skin are made to facilitate lymphatic drainage but this procedure is not recommended in permanent varices since it exposes the patient to other infection It is indicated merely to decrease the tension of lymphatic edema (Napier) Major surgical intervention is used purely in indicated cases such as extirpation in huge elephantiasis of the scrotum or of the breast (Anchieloss operation etc) Chyluria is treated by complete rest suppression of fats in the diet and administration of salines (laxatives)

Loa Loa—Culbertson et al observed both diminution of circulating microfilariae and improvement of clinical symptoms following administration of Neostibosan in 3 loiasis patients Shookoff noted clinical improvement in 3 cases of Loa infection after treatment with Hetrazan

Treatment of Onchocerciasis

Treatment of onchocerciasis is not yet efficient The following procedures have been suggested surgical extirpation of the largest possible number of nodules to prevent possible ocular complications this is not practicable when the number of nodules is very great Interstitial injections of the nodules using gentian violet or hexylresorcinol bichloride of mercury Intravenous injection of tartar emetic Plasmochin (0 1 per cent solution) into the anterior chamber of the eye Radiotherapy local diathermy and electrocoagulation etc have not as yet been sufficiently tried

Van Hoof et al employed Bayer 205 (urea of acid dimeta aminobenzoyl meta aminoethyl benzoyl 1 naphthylamino 4 6 8 trisulphonate of sodium) in treatment of onchocerciasis

Hetrazan seems very active against Onchocerca but may produce severe reactions Both of the above may give allergic reactions upon death of the adult worms and microfilariae Optimum dosage is not as yet established Burch reported 50 patients treated with Bayer 205 Patients were rendered free of microfilariae and the adult worms are killed One half of the patients experienced severe burning of the feet ⅓ showed pruritis and cutaneous induration ½ developed photophobia lacrimation and burning of the eyes frequently accompanied by conjunctival and episcleral injection

In the 50 patients treated by Burch with Hetrazan the microfilariae also disappeared but the effect on the adult worm is not as satisfactory as with Bayer 205 Reactions to Hetrazan were also more pronounced About ⅓ developed skin eruptions in addition to one or more of the reactions mentioned above Toxic manifestations were more severe in advanced cases of onchocerciasis Caution must be used in the administration of both drugs

Treatment of Trichinosis

Refer to Chapter 38 Treatment of trichinosis is not very effective In many cases the symptoms are very slight and do not demand treatment

Treatment of Schistosomiasis

Success in the treatment of schistosomiasis depends upon whether it has been applied in the initial period or later after definite sclerotic organic lesions have already been produced It consists principally in the administration by injection of salts of antimony tartrate of antimony and sodium or tartar emetic or Fuadin injected as in visceral leishmaniasis The pentavalent antimonials are much less efficacious In schistosomiasis mansoni it is necessary to repeat the antimonial several times with an interval of 1 week or several weeks to obtain sufficient improvement or cure In advanced cases treatment is not successful or the results may be very incomplete

In patients with advanced or chronic schistosomiasis injection of antimonials usually causes hepatic disturbances (bilirubinemia icterus etc) according to Cawadias and others The majority of authors however agree that Fuadin is absolutely harmless even in the cirrhotic livers of the chronic patients (Kahlil Salah and Hassan) Emetine hydrochloride has also been used in the same manner as in amebic dysentery but with uncertain results

Brown (1948) referred to the work of Alves and Blair (1946) on an intensive or 1 day treatment of schistosomiasis with sodium antimonyl tartrate They used a continuous drip technic which they later abandoned for the multiple syringe method of intravenous injections 3 times daily at 3 hour intervals for 2 days—a total of 6 injections This was on the basis of 1 grain for each 12 pounds of body weight On the basis of the skin test using cercarial antigen and examination for eggs the authors considered the rapid treatment successful in a high percentage of their patients Halawani of Egypt (Brown 1948) reported his experiences with Fuadin At the Fouad Institute they used Fuadin intramuscularly giving 30 to 33 c c in 2 days with less toxic reactions Fuadin is definitely less toxic than tartar emetic Brown is employing in Egypt at the present time a modified intensive method consisting of administration to adults of 5 c c of Fuadin daily for 10 days Regarding the new drug Miracil D which is a thioxanthone derivative Brown believes that the unsatisfactory results hitherto obtained were due to the administration of inadequate doses At the Fouad Institute cures of bilharziasis cases occurred after administration of 0 5 Gm daily morning and evening for 7 to 8 days

In the treatment of schistosomiasis japonica Billings and others (1948) reported on 110 patients treated with 40 c c of Fuadin of whom 19 relapsed within 4 to 8 weeks In a further report on 210 patients treated with this same dosage of Fuadin Winkenwerder and others noted relapses in approximately 40 per cent after 4 weeks observation Seitz used the technic of Alves and Blair in 320 cases and reported failure in only 3 of 216 cases followed for 8 weeks Toxic reactions were avoided by dilution of the drug and slowing of the rate of injection

Most (1948) discussed schistosomiasis japonica acquired by the American personnel on the Island of Leyte Approximately 1 500 men were hospitalized and treated for schistosomiasis japonica on Leyte These patients were returned to the United States for operation and treatment An equal number of men contracted this disease on Leyte and were not hospitalized In addition to these men approximately 2 000 officers and enlisted men who were imprisoned in a penal colony at Davao on the Island of Mindanao had an infection rate among them of about 50 per cent Most reported failure of Fuadin in these cases even when total doses of 70 and 105 c c were given

Treatment of Clonorchiasis

Treatment of clonorchiasis may be successful if initiated early It consists in oral administration of gentian violet Antimony and sodium tartrate or tartar emetic have also been used in the same manner as in kala azar and gold salts by intravenous injection After the infection has reached an advanced stage with cirrhotic fibrotic lesions cure is very difficult

Treatment of Hepatic Distomatosis or Fascioliasis Hepatica

The most efficient treatment consists in intramuscular injections of emetine hydrochloride (Kouri and Basnuevo) Serial examination of the bile obtained by duodenal intubation is used to control the treatment Carbon tetrachloride tetrachloroethylene and other drugs have also been used

TREATMENT OF BITES OR STINGS OF VENOMOUS ANIMALS

Treatment of bites of venomous snakes of America and treatment of accidents caused by arthropods are discussed in other chapters (Chapters 55 to 58 inclusive) and will not be repeated here

Treatment of Scabies

Treatment of scabies includes the application of various topical parasiticides It is debatable whether or not a bath should be given at the commencement of treatment Some authors (Dixon 1941) state that scabies may be cured simply by a good soap bath and friction According to Mellanby, a previous bath is not considered indispensable but convenient and may facilitate penetration of the medicament

Recently tetraethylthiuramammonosulphide (Tetmosal) has also been used in a 5 per cent solution applied once or twice a day It is well tolerated (Clayton 1943 Bradshaw 1944 Wilshaw 1945)

Sulfur has been used as sulfo oleates sulfo ichthyolates (Ichthyol Thiogenol tumenol etc) in the form of unguents Some of the commercial specialty preparations for scabies contain these sulfo oleates All of these sulfur preparations have a keratolytic action are parasiticidal and have a decongestive action upon the skin They have been used for many years in the treatment of scabies An advantage is that they are economical in cost but in recent years there has been a tendency to substitute other medicaments

Benzyl benzoate a dense aromatic oily liquid insoluble in water miscible with alcohol is used in scabies in the form of a lotion with equal parts of alcohol and soft soap

Rub it on for 5 minutes let it dry rub again and dress A bath is taken in 24 hours This medication does not soil the clothing is easy to apply and is well tolerated

Bedker and Obermayer recommended a benzyl benzoate lotion and a sulfur Peruvian balsam ointment

℞	Soft Soap	
	Isopropyl (or ethyl alcohol)	
	Benzyl benzoate	
	aa qs ad 120 cc	

℞	Precipitated sulfur	12 0
	Peruvian balsam	12 0
	Petrolatum	
	Hydrous wool fat	
	aa qs ad 120 cc	

The cost of these preparations is a major disadvantage in South America

Skin infections should be treated by slightly antiseptic baths warm followed by application of powdered sulfanilamide

Impregnation of clothing with DDT is usually ineffective for the destruction of acarids (Heller) The simple warm soapy bath prolonged and repeated daily constitutes a good prophylactic and Mellanby advises 10 per cent Tetmosal soap In seborrheic individuals the most frequent and troublesome complication is pyogenic infection of the skin which may be treated with weak antiseptics or preferably with sulfanilamide in powder form or 5 per cent ointment

Application of a topical antipruritic medicament may be necessary to quiet the pruritus which is intense in some cases Mixtures of phenol menthol equal parts in a lotion or of phenol camphor 10 per cent lotion or unguentum or of menthol or thymol 1 per cent in diluted alcohol are efficient Obermayer recommends the following antipruritic shake lotion

℞	Menthol	0 5
	Phenol	0 5
	Zinc oxide	20 0
	Talc	20 0
	Glycerin	15 0
	Water	00

Treatment of Pediculosis The Body Louse

Treatment requires frequent changing and disinfection of underclothing and bedding Clothing is readily disinfected *with dry hot air 5 minutes at* 55° C , or simply by hanging the clothing in the sun in dry air for several hours or with water vapor at 90° 100° C from a spout for 10 minutes or hot water at 60° to 70° C for 5 minutes or by immersion in cresol solution (2 per cent solution) for 30 minutes which is efficient but inconvenient because of the strong carbolic acid odor or by fumigation with various chemical substances

Clothing may also be disinfected by impregnation with other substances preparations of pyrethrum (Jones et al 1944) thiocyanate (Busvine 1945) and especially DDT which is very efficient and not very dangerous

Application of insecticides upon the skin is not so essential since the insect lives in clothing Dusting with DDT is useful using it in powder form 10 parts with 100 parts of inert powder and using an adequate duster (see various types of dust sprayers in Higgins 1945)

Treatment of Pediculosis of the Head The Head Louse

Treatment is generally not difficult but reinfestation must be prevented since groups especially children or families are readily reinfested First a good washing with soap and water then application of insecticide constitutes the procedure Washing and rubbing with 1 1 000 solution of bichloride of mercury is repeated for 2 or 3 days (danger of dermatitis) or application of equal parts of kerosene and olive oil to be left on overnight followed by washing the following morning or application of kerosene and vinegar for 1 or 2 hours or of a lotion composed of 40 per cent phenyl cellosolve 30 per cent ethanol 25 per cent water with 5 per cent methyl salicylate (left in the hair for 2 or 3 days while protecting the eyes) or pulverized pyrethrum in kerosene or rubbing with an emulsion of DDT (Scobbie 1945) which seems to be very efficient The procedure of Sabouraud (1935) is also effective This consists in keeping a rubber cap on the head overnight with pure petroleum jelly or petroleum jelly with 10 per cent benzine followed the next day by thorough washing It should be followed by combing with a fine comb repeatedly Application of a 1 per cent emulsion of rotenone for several hours is followed by washing Good commercial preparations such as Cuprex and Kwell are available and recommended by many authors

In treating the delicate scalp of a child it is necessary to proceed cautiously Unguents of 5 per cent naphthol in adeps or 5 per cent salicylic acid solution are used (see Buxton 1940)

Treatment of Pubic Pediculosis The Pubic Louse

The parasite is readily detachable by simple pinching It causes pruritus *It can be destroyed readily by many topical insecticides* but the genital region is very sensitive and easily irritated and this is the principal difficulty in treatment (dermatitis medicamentosa) Almost any mercurial ointment

is effective if maintained for a sufficiently long period (several hours) 5 per cent yellow oxide with petroleum jelly lanolin 30 per cent calomel with petroleum jelly lanolin (advantage its white color), mercurial ointment (the old gray ointment) but the dark color which injures clothing is objectionable although it is very efficient a simple 0 5 per cent lotion of bichloride of mercury applied by friction without drying twice a day repeated twice is efficient it does not spot clothing but is not well tolerated by some skins (transient dermatitis) 2 per cent oxyneurine lotion 2 per cent Mercurochrome (objectionable because of its red color) Petroleum is also efficient (bad odor) alone or mixed with a balsam applied with cotton at night, xylol 20 per cent in petroleum jelly or 10 to 20 per cent in alcohol and ether 10 per cent naphthol in daily applications Various good commercial preparations are obtainable (Cuprex Kwell etc)

Pediculosis of the eyebrows must be treated with great care but repeated rubbing with concentrated lotion of bichloride of mercury is effective

TREATMENT OF CUTANEOUS AND VISCERAL MYCOSES

(Tinea, Dermatophytosis, Sporotrichosis, Blastomycosis)

The physician has at his disposal the following agents and therapeutic means

1 **Surgical treatment**

2 ***Roentgen ray therapy***

3 **Internal medication with iodine**

4 **Internal medication by sulfanilamide derivatives** is administered in large doses in the usual form by ingestion The initial dose is 2 to 4 Gm and then 1 Gm every 4 hours according to the intensity of the treatment and the patient s tolerance The patient must drink large quantities of water to prevent precipitations of the drug in the kidneys Efficacy is inconstant but in some cases good results have been obtained in actinomycosis maduromycosis blastomycosis

5 **Other internal medications** are antibiotics especially penicillin and streptomycin Externally Fradicin Prodigiosin and Furaspor

6 **Vaccine therapy,** which is only desensitizing

Treatment of Certain Forms of Cutaneous Mycosis

In areas of thin skin (glabrous skin) the application of topical medication generally suffices In thick skin areas (palm of the hand sole of the foot) previous application of exfoliating topical medication for the purpose of removing the superficial epidermis may be necessary This may be accomplished by a prolonged warm alkaline or sulfur bath In addition there are 3 drugs which may be used chiefly to obtain this keratolytic and exfoliating effect salicylic acid (in benzoic salicylic solution e g in the classical Whitfield ointment) potassium combinations (all the alkalines) and resorcinol (or pyrogallol in ointment or solution) Sulfur also may be keratolytic

With hairy skins it may be necessary to pluck the hair (manual epilation with tweezers or by radiotherapy).

The most common antimycotic topical medications include iodine (tincture, Lugol's solution, solution of iodine in chloroform or acetone), salicylic acid (4 per cent in alcohol or combined with benzoic acid in lanolin and petroleum jelly or in alcohol ether), chrysarobin (in ointment or unguentum 1 or 5 per cent in petroleum jelly or lanolin), mercury (simple unguentum, double unguentum, 5 per cent mercuric ammoniacal ointment, 1 per cent bichloride of mercury solution), resorcinol, pyrogallol, sulfur (2 per cent ointment in petroleum jelly). Prodigiosin and Fradicin are effective.

Secondary infection is frequent (in the feet and scalp) and is treated preferably with oxidizing antiseptics: 1:4,000 solution of potassium permanganate baths or compresses left on overnight. Sulfanilamide is usually not effective. Absolute cleanliness is indispensable.

CHAPTER 65

THE USE OF ANTIBIOTICS IN TROPICAL DISEASES

OSCAR FELSENFELD AND SACHIKO JANET ISHIHARA

While this book was being prepared for publication, a series of new antibiotics was discovered and introduced in the treatment of tropical diseases. Thus it became imperative to add a short summary recording recent progress in these therapeutics from data available as of January, 1950.

Penicillin is still the queen of the antibiotics. It is widely (and unfortunately often indiscriminately) used, mostly in the form of benzyl penicillin (penicillin G). One can find on the market crystalline potassium penicillin, a soluble salt which rapidly gives high blood levels but of short duration, procaine penicillin which is slowly liberated, thus producing lower blood levels of long duration, and combinations of both which are frequently used as once a day injections. This combination usually contains 100 000 units of potassium penicillin and 300 000 units of procaine penicillin in each c c. With the exception of some cases of syphilis, meningitis, subacute bacterial endocarditis, psittacosis, chronic suppuration, tetanus and gas gangrene, 1 to 2 c c of the combined penicillins will suffice for the treatment of most conditions in which this drug is indicated.

Penicillin, however, causes allergic reactions in certain cases. A new biosynthetic penicillin called penicillin O (allylmercaptomethylpenicillin) may be given to patients hypersensitive to penicillin G (Volini et al 1950).

Penicillin in properly protected form can be administered orally. In order to obtain blood levels comparable to those obtained on injection, the oral dose has to be 8 to 10 times higher.

Organisms often become resistant to penicillin. It is necessary, therefore, to check frequently the sensitivity of the causative organism against antibiotics during penicillin treatment.

Streptomycin, if used carefully, is an excellent drug. Safe in purely intestinal infections, as in shigellosis, it should not be given orally because it is poorly absorbed from the intestines.* One Gm per day is given in chronic infections, as in tuberculosis, while 2 Gm per day are indicated in acute diseases. Streptomycin should not be given for a longer period than 10 weeks.

Streptomycin often causes allergic reactions and damage of the liver, the vestibular apparatus and the eighth nerve. Dihydrostreptomycin is much less toxic. Glucomycin is a nontoxic oral form of streptomycin.

Chloromycetin (Chloramphenicol) is but little soluble and is given per os (Ehrlich et al 1947, Smadel and Jackson 1947, Woodward 1949, Knight et al 1949). The initial dose is 3 to 5 Gm, followed by 1 to 3 Gm per day

*Oral streptomycin is, however, indicated when the intestinal flora has to be reduced, e g before operation.

Chloromycetin according to present experience seldom causes unfavorable side effects. The authors have observed oppression of the hematopoietic apparatus under prolonged dosage. The antimicrobial spectrum of Chloromycetin includes Rickettsiae and some large sized viruses. While Chloromycetin is a drug causing immediate therapeutic effect in infections with many gram negative organisms, relapses are not infrequent in subacute or chronic cases.

Aureomycin (Woodward 1949, Knight et al 1949, Duggar 1948, Schoenbach et al 1948, Brainerd et al 1949, Greenblatt et al 1948, Spink and Yow, 1949) is an excellent drug which is indicated in approximately the same diseases in which Chloromycetin has been used. It is most frequently administered per os 2 to 3 Gm per day. It may cause gastrointestinal disturbance and in such cases has to be given intravenously 2 Gm per day. Because of its excellent effect on a number of viruses it is being widely used.

Neomycin (Waksman and Lechevalier 1949, Felsenfeld et al 1949, 1950) is a drug with a great future. It resembles streptomycin but has a much wider therapeutic spectrum which includes also protozoa. While many organisms become streptomycin resistant during streptomycin therapy, neomycin does not seem to have such an effect on microbes. The authors together with Drs Kadison and Volini of Cook County Hospital have observed satisfactory results in tuberculosis (especially in extrapulmonary forms), salmonellosis, brucellosis, amebiasis, infections with *E coli*, *A aerogenes*, Pseudomonades, Protei and other conditions, injecting intramuscularly 50 000 to 200 000 units per day. The oral dose is 10 to 20 times larger than the intramuscular dose. Kidney irritation and disturbance of the vestibular apparatus were seen however after injections. The oral dose is about 120 000 units per day in amebiasis.

Polymyxin D is active against many organisms (Benedict and Langlykke 1947, Stansley et al 1947, Felsenfeld et al 1949, 1950) but still has not been deprived of its nephrotoxic activity. In view of its strong antiviral and antirickettsial activity it is felt that polymyxin D should be kept on the record.

Bacitracin (Johnson et al 1945, Meleney and Johnson 1947, Derzavis et al 1949, Felsenfeld et al 1949, 1950) is used topically in pyodermas, injected in gas gangrene and given per os in amebiasis. The oral treatment of amebiasis consists of 60 000 to 120 000 units per day for 10 to 14 days (Most et al 1949). Because of the possible nephrotoxic action in cases where bacitracin injections are indicated (adjuvant treatment of syphilis and subacute bacterial endocarditis during penicillin therapy) a smaller dose of 12 000 to 25 000 units is injected intramuscularly per day for 10 to 14 days. Bacitracin is also indicated in smallpox and cholera.

Many other antibiotics such as *subtilin*, *circulin*, *Fradicin* are still being investigated because of their toxicity, others such as *gramicidin* and *tyrocidin* are used only externally.

Table XXX shows the results of the efficacy of antibiotics in tropical diseases according to present experience and literature.

Combinations of antibiotics, also with sulfa drugs, may be of value. Bacitracin strongly potentiates the action of penicillin on cocci and Trepone

mataceae. Mixtures of bacitracin and neomycin or polymyxin D per os are very *effective against bacterial infections and amebiasis*. If sulfa drugs are given with penicillin or streptomycin the organisms have a lesser tendency to develop resistance toward the drugs. BAL also increases the efficacy of many antibiotics, especially that of streptomycin, Chloromycetin, *aureomycin* and neomycin. Thus combinations of drugs may be used, especially to treat infections with microorganisms which are resistant to one or another antibiotic.

Needless to say, antibiotics shall never be used in a haphazard way but only after proper laboratory tests are carried out. Unfortunately in vitro experiments with Treponemataceae are difficult to set up, even impossible with *T. pallidum*. In an emergency penicillin should be given but material for bacteriologic examination has to be collected before the first injection is administered. Aureomycin and neomycin are other drugs which can be injected, especially when suspicion of an infection with a gram negative organism arises before the laboratory report is received. It must be emphasized, however, that these are emergency measures applicable to pneumonia, meningitis, typhus and similar conditions, never to a subacute or chronic case.

Prodigiosin is known to be applicable internally against systemic infections with molds and fungi, while externally *Fradicin* is very effective (Felsenfeld et al., in press). Against blood flagellates only Prodigiosin and combinations of antibiotics with arsenicals and BAL are promising. One has to keep in mind that some antibiotics inhibit enzymatic function of bacteria. Viruses, especially small viruses, parasites and fungi do not have to be checked necessarily if the enzymatic function in question is inhibited by the antibiotic. Thus further search for therapeutic agents is still warranted and desirable.*

TABLE XXX. EFFICACY OF ANTIBIOTICS IN THE TREATMENT OF TROPICAL DISEASES

INFECTIONS WITH	PENICILLIN	STREPTOMYCIN	CHLOROMYCETIN	AUREOMYCIN	NEOMYCIN	POLYMYXIN D	BACITRACIN
K. rhinoscleromatis	I	U	U	U	I	I	I
Salmonella	I	C	U	C	I	I	I
Shigella	I	U	U	I	E	E	I
Brucella	I	C	C	U	C	E	I
Pasteurella	I	I	E	E	I	I	S
Vibrios	I	S	C	C	I	C	U
Malleomyces	I	U	I	E	E	E	I
Myco. tuberculosis	I	C	S	S	I	I	I
Treponema	E	I	C	C	C	S	E
Leptospira	I	U	E	I	I	I	S
Borrelia	U	E	E	E	E	I	S
Spirillum	I	C	C	C	C	C	S
Bartonella	E	C	E	E	I	E	I
L. inguinale	I	I	E	E	I	I	U
Psittacosis	U	I	U	U	C	C	C
Pox group	I	I	S	C	C	C	U
Granuloma inguinale	I	U	U	E	E	I	U
Rickettsia	I	I	E	E	I	I	I
Actinomyces	C	S	U	U	C	C	I
E. histolytica	I	I	C	C	E	S	C

E, effective; C, effective against certain strains; I, ineffective; U, usually effective; S, seldom effective.

* After this chapter was written, terramycin was introduced. Its action resembles that of aureomycin.

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CHAPTER 66

HYGIENE IN THE TROPICS

GEORGE MURDOCH SAUNDERS

INTRODUCTION

Hygiene has been defined as the science of preserving and promoting health It encompasses not only the prevention of disease but also those factors which promote the highest mental and physical well being To discuss in a single chapter of limited length all factors bearing on healthy living in the Tropics would be an impossibility, for hygiene in tropical environments must include not only a consideration of all factors which concern well being outside the Tropics but a host of others which are peculiar to hot countries General factors which are important health forces in the Tropics will be discussed, and reference will be made only briefly to the prevention of particular diseases as more detailed discussions will be found in other chapters A knowledge of the fundamental physiologic responses to altered climatic conditions are necessary for a clear conception of tropical hygiene and must be explored in some detail The control and alteration of environmental elements such as housing clothing, diet, water supplies, sewage, and refuse disposal will be mentioned briefly

HISTORICAL BACKGROUND

Man has lived and prospered for thousands of years on all of the large land masses of the earth and in such greatly diverse environments as the cold barren Arctic wastes and the hot wet jungles of equatorial Africa and the Amazon basin In fact, high degrees of civilization, as indicated by the development of arts crafts, and sciences, have been reached by peoples living in tropical and subtropical regions The Egyptians, the Mayans, and the Cambodians may be cited as pertinent examples of vigorous, progressive civilizations which endured for centuries under conditions which, by today's criteria might be called unsuitable for the maintenance of a high standard of civilization

However, most of these ancient examples of man's triumph over environment were unknown or forgotten when, only about 500 years ago men living in Europe began to carry the benefits of "modern civilization to the unknown lands to the south east and west The empire building nations carried European diseases to the "new" lands, and in turn they were confronted by new and trying climates and many mysterious ailments which were often fatal Fevers carried off staggering numbers of the colonists and were attributed to miasmas arising from the swamps, insects and snakes were pestilential, and the damp heat of the jungle was not a comfortable habitat for men dressed in wool and armor It is not surprising that for hundreds of years the Tropics were dreaded and maligned by the Europeans who explored plundered, and developed the hot countries urged by the desire for gold and spices, or simply by the spirit of adventure

Fear of the unknown conditioned the attitude of men toward the Tropics, which for so long were considered unsuitable for habitation by European peoples Medical books written a century ago, and many since, stressed the deteriorating influence of tropical

climates on the northerners. This attitude has been slow to change, in spite of new scientific knowledge which has explained rationally the cause of many formerly obscure diseases and has offered wide relief by preventive and curative measures. Because many of those who wrote about the Tropics were reared and educated in temperate zones and had only temporary residence in tropical areas they commonly carried their prejudices with them and in subsequent writings fostered the idea of the malignant influence of tropical climates. They were the advocates of cumbersome, heavy headgear of cork or other materials with red lining and thick felt or woolen spine pads for protection against the "deadly red rays" of the tropical sun. Cholera belts were recommended to prevent the abdomen from becoming chilled by the cold night air which was thought to precipitate cramps or enteritis. Neurasthenia was believed to be inevitable in at least one third of the northern sojourners in the Tropics, but it was blamed on the new environment and especially the climate.

Factual knowledge of disease has gradually dispelled most of the mysteries of tropical ailments, and many conditions formerly thought to be caused by climate have been found to be the result of definite disease processes. About 40 years ago, in a book on climate and health in hot countries Giles (1905) wrote, "a hundred years ago a prolonged residence in the tropics was regarded with well founded horror. The best the white settler in the lands of the sun dared hope for was 'a short life and a merry one,' but too often the merriment was sadly lacking. . . . But with due care and attention to sanitary laws, as modified by the altered conditions, there is no reason why the rates of sickness and mortality should be more formidable than elsewhere."

Prejudice dies hard, however, and there are still too many fallacious statements made regarding the dangers of life in the Tropics, particularly concerning the ill effects of the climate itself. Many commentaries on tropical hygiene have been written from the viewpoint of the northerner, who may or may not have had extensive experience in hot countries, and they have stressed unduly, the deleterious effects of tropical environment on temporary residents. It is felt that a more logical approach is to consider man, generally, in relation to the special hygienic forces found in tropical areas. There are many regions within the tropical belt in South America, Africa, and in the East Indies where the inhabitants follow from day to day the normal ordinary habits of modern life in comfort and health unaware of the many dangers supposed to surround them and of the concern shown for their welfare by sanitarians of the North. Tropical medicine has gone through its birth, infancy, and adolescence in the past 75 years. Causative agents of disease and intermediate hosts have been identified and methods of prevention have been developed. Control of disease permits northern as well as indigenous racial groups to inhabit and prosper in vast areas formerly thought uninhabitable (Todd, 1924).

THE TROPICS DEFINED

There have been many definitions of what constitutes the Tropics and many classifications of different kinds of tropical climates based largely on mean annual temperatures, humidity and wind conditions, altitude and proximity to the sea. The true mathematical tropics include, of course, all that territory between the Tropics of Cancer and Capricorn from 23½° N to 23½° S latitudes. But there are areas within this zone where because of altitude or cold ocean currents and cool winds, conditions are temperate. Furthermore, in many localities outside these limits conditions are tropical.

Supan's (1927) classification, suggested in 1896, is frequently referred to in works on the subject. He extends the Tropics or warm climates from the equator to the mean annual isotherms of 20° C (68° F), which gives a northern limit of about 35° N and a southern limit of less than 30° S. Subtropical regions are included within isotherms of 20° C (68° F) for the cold

months This classification includes the southern part of North America, Mexico, the Caribbean area, a considerable portion of South America, much of Africa, Asia Minor, Iran North India, China, Australia, and the intervening islands Others, including Koppen (1900), took as a criterion a temperature of *more than 20° C (68° F) for all 12 months of the year Price (1939) adopted* a mean annual isotherm of 21° C (70° F) as the limits of the Tropics

There can be no hard and fast rule as to what territory should be included in a definition of the tropical areas For hygienic considerations it should include those areas which have hot weather throughout most of the year The mean annual isotherm of 21° C (70° F) is probably the most suitable for our purpose The mean annual temperature in the equatorial zone is about 27° C (80° F), with greater maxima and minima farther away from the equator It must be remembered that many places outside the Tropics, for example, St Louis or Washington, D C, in the United States, have higher temperatures during the summer than many low lying places close to the equator

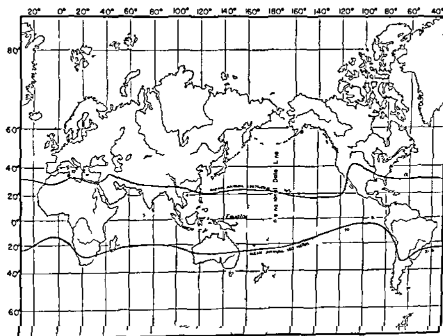


Fig 437 —World map showing area of tropics as limited by mean annual isotherms of 21° C (70° F)

There are great variations in climate in the tropical zone Of the numerous classifications of types of climate which have been suggested, perhaps the simplest is to divide arbitrarily into the hot-wet or jungle areas, the hot dry or desert areas, and the high cold or mountain areas If heat is essential to "tropics" then it is obvious that mountain areas are not truly tropical

Among the many factors important in determining climate and weather conditions, water, winds, and elevation are perhaps the most important Water, *because of its high capacity for heat*, is a great thermal stabilizing

influence In jungle areas climatic conditions are fairly constant with a mean annual temperature of about 27° C (80° F) or more and high relative humidities of 80 per cent or more There is little daily or seasonal fluctuation largely because of the influence of water in the earth in the air and in the dense vegetation The amount of insolation or sun s rays reaching the earth is also affected by moisture in the air and by the vegetation The longer light waves are largely dispersed and absorbed by moisture in the air and by the heavy vegetation The waves at the short end of the spectrum however are but little affected by the moisture content of the air although ozone which scatters and absorbs the ultraviolet rays to a certain extent is apt to be found in higher concentration where there is dense vegetation (Blum 1945)

In hot desert climates the characteristic features besides low or absent rainfall and low relative humidity are large and regular diurnal temperature cycles intense sunlight and occasional strong winds The ground is dry its specific heat is low and in the absence of water to vaporize surface temperature may reach 84° C in the midday sun cooling rapidly after sunset The air temperature shows large swings from less than 20° C (68° F) at night to 45° C (114° F) or more at midday The sun s rays are strong with little scattering or absorption by the atmosphere or vegetation

In mountain climates the temperature varies inversely to the altitude For every increase of 300 feet of altitude there is a decrease of about 1° F i e for every 180 meters a decrease of 1° C These figures are only generally true however for other factors such as humidity the clearness of the atmosphere and air currents also influence temperature (Strong 1943) It is easy to understand how one of two locations of equal latitude and only a few miles apart might have a jungle climate with a mean temperature of 27° C (80° F) while the other might have a mean temperature of 18° C (66° F) or less The lower temperatures of mountain climates may have an important bearing on disease prevalence for they may be below the critical level for mosquitoes and possibly other arthropod vectors of disease Since the sun rays are filtered out to a certain extent by the earth s atmosphere the intensity of radiation increases with altitude showing a relatively greater increase at the two ends of the spectrum Thus the heating effects of the infrared rays and the sunburning effects of the ultraviolet rays become more evident in mountain climates

PHYSIOLOGIC ASPECTS OF TEMPERATURE REGULATION

There is a nice adjustment of heat loss and heat production in man to maintain a nearly constant body temperature of about 37° C (98.6° F) in the face of wide variations in environmental temperatures An understanding of the basic processes involved is essential for a proper evaluation of reactions to climate

Heat production is the result of oxidation processes within the cells of the body There is a normal minimum heat production which is very nearly constant for man under so called basal conditions of rest fasting clothed

and in a comfortable environmental temperature This basal metabolic rate or B M R is usually expressed in kilogram calories per square meter of surface area or per kilogram of body weight per hour For a normal adult male the B M R is about 40 kg cals/m^2/hr or 1 kg cal/kg/hr This basal rate is affected by various factors The B M R of women is usually 7 to 12 per cent less than that of men The rate is much higher in infancy and childhood decreasing rapidly after puberty to the adult level and decreasing very slowly thereafter to old age Physical exertion shivering mental activity certain drugs and disease processes all serve to increase metabolism Food stimulates basal metabolism and the "specific dynamic action" is a factor to be considered Proteins may increase metabolism by 20 to 30 per cent and carbohydrates and fats from 5 to 10 per cent (Wiggers 1944)

Under basal conditions the normal adult male is producing heat at the rate of about 1 700 kg cals in 24 hours This increases to 2 500 calories for persons of sedentary occupations and may go as high as 5 000 calories as heat production of the body is increased through muscular activity or other means The oxygen consumption and the output of the heart increase proportionately At rest the heart may be pumping to the tissues about 4 liters of blood per minute carrying 240 c c of oxygen With violent muscular activity the output of the heart may increase to nearly 25 liters per minute representing 3 liters of oxygen The metabolic rate and the production of heat is multiplied many times Under certain environmental conditions the body may gain heat by radiation conduction or convection Gains by radiation from direct sunlight or from heated objects may be great, and Martin (1930) figured that on a sunny day his nude body would absorb heat at the rate of more than 3 kg cals/min or 3 times his resting heat production In spite of a greatly increased heat production there is little increase in body temperature because of two important factors First, because the body has a higher water content it has a high specific heat value which permits a relatively large absorption of heat with a small temperature increase, and second because of the presence of the efficient and sensitive temperature regulatory mechanism of the body

All heat produced must be dissipated if body temperatures are to remain relatively constant It is well recognized that even mild exercise increases body temperature which soon returns to normal during rest (Brennemann 1943) This indicates a temporary accumulation of heat which is soon dissipated by normal processes

Heat may be lost from the body by radiation by conduction and convection to the environment if the environment is cooler than the body and by evaporation of water A small amount is also lost in the urine and feces At environmental temperatures of less than 28° C (83° F) the major portion of heat loss occurs through radiation some through conduction and convection and only about 25 to 30 per cent through vaporization Some heat loss through vaporization occurs in the absence of any activity of the sweat glands Water is lost as vapor in the expired air in amounts estimated from 250 c c to 400 c c and by "insensible" perspiration in amounts of 600 c c to 800 c c

in 24 hours for a total of about a liter a day (Dill 1938) At body temperatures this represents a heat loss of about 580 calories (Wulsin 1943)

However as environmental conditions change with increasing temperature heat loss through vaporization increases and may represent a large portion of total heat loss Careful calorimetric studies on nude subjects were recorded by Hardy and Soderstrom (1938) They concluded there is a neutral temperature range for nude human beings in the basal state of 28° to 31° C when heat loss is at a minimum There is a 'cold zone' from 22° to 28° C at which there is no physiologic regulation of heat loss the body cooling as an inanimate object In the cold zone vasomotor effects are insignificant vaporization is constant and proportional to the surface area and the thermal conductivity of surface tissues and peripheral blood flow are about constant In a temperature range from 28° C to 30° C the zone of vasomotor regulation at which heat loss is at a minimum there is increased peripheral circulation but vaporization is still constant This zone was the most comfortable to the subjects Above 30° C the blood flow to the skin and the vaporization increase directly with the temperature of the environment sweating begins to play a part in the cooling process at about 30° C During the experiment the rectal temperatures increased 0 2° C for each 1° C increase in calorimeter temperatures Skin temperatures also increased from about 31° C to more than 34° C as calorimeter temperatures rose from 23° C to 35° C Heat loss was approximately equal to heat production only in the narrow range from 29° C to 32° C (85° F to 90 F) at other temperatures heat loss was greater than heat production and declined rapidly to its lowest level as the calorimeter temperature rose from 22° C to 28° C and then increased more slowly as the environmental temperature rose above 32° C The vaporization of moisture was nearly constant up to 30° C above which it increased rapidly with temperature

MAN S REACTION TO A HOT ENVIRONMENT

During the past few years numerous studies have been made designed to test man s adaptability to the hot dry heat of a desert climate and to the hot wet heat of a jungle climate (Dill 1938 Taylor et al 1943, Henschel et al 1943 Soleman and Lurch 1944 Robinson et al 1941 Machle 1944) Most of the studies were carried out in laboratory heat chambers where any type of climate could be simulated and careful observations could be made As a result certain important conclusions have been reached

As environmental temperatures rise there are prompt physiologic responses which are similar in resting and in working subjects which increase quantitatively with environmental temperatures and with the degree of physical activity The responses represent the body s attempt to maintain a normal temperature by stimulating increased heat loss There is increased peripheral blood flow with peripheral vasodilatation This requires greater cardiac output and at times the heart rate increases to as much as 180 beats per

minute Internal and skin temperatures rise but because the greatest increase is internal the thermal gradient from deep tissues to skin surface is larger This favors heat loss through radiation conduction and convection *provided the environment is cooler than the skin surface* Sweating increases the amount of surface water available for vaporization and as much as a liter per hour may be lost during work at high temperatures representing a cooling of 580 calories *As environmental temperatures equal or exceed the body surface temperature heat loss by other means than vaporization may become negligible and heat gains may result* Therefore the amount of water vapor *in the air the relative humidity or the wet bulb temperature becomes the most* important factor in heat loss at high environmental temperatures If no vaporization can take place because the environment is saturated with water vapor *the last remaining mechanism for dissipating heat is lost and there is* complete breakdown of temperature regulation This condition results in hyperthermia which is fatal if unchecked

Under conditions of thermal stress the two most effective regulatory mechanisms are circulation and sweating There is a double strain put on the heart in regulating temperature because peripheral circulation must be accelerated for cooling and any rise in body temperature which accompanies heat stress means increased metabolism with greater oxygen requirements and hence further acceleration in the circulation of blood is demanded Therefore the efficiency of the cardiovascular system is the most important factor in limiting adaptation to heat As the circulatory limits vary considerably with individuals so does the ability to adjust to heat

The amount of sweat produced is also a factor in adjustment to heat and persons who sweat most adapt best to heat and have a smaller rise in body temperature than those who sweat little Body temperature may rise 2° C to 3° C or more under conditions of thermal and physical stress

As thermal stress increases the heart rate becomes more and more rapid and may reach the limit of 180 beats per minute *Dizziness and stupor may* result as well as vasomotor instability as evidenced by *low blood pressure* and fainting on changing to an erect position Body temperatures may climb to dangerously high levels and collapse may ensue During this period there is profuse perspiration although this mechanism *too may break down as* collapse approaches Cramps in the muscles or in the abdomen may also occur

There is a loss of water and chemical substances chiefly salt urea and lactate in sweat with a resulting change in various *constituents of the blood* and tissues Dehydration a lowered concentration of sodium and chloride ions in the plasma diminished urinary output with little or no sodium chloride in the urine and an *increased serum protein concentration and red cell* count may result

It has been shown that man adapts better to heat conditions and becomes more efficient *in his thermal regulation after relatively short acclimatization* periods of a few days to a week or more Sweating becomes more profuse starts more rapidly upon exposure to heat and the concentration of salt in sweat *decreases The temperature rise is less marked after a few days of*

"training" in the heat, and may be less than 1° C where it was more than 2° C before acclimatization, indicating an improvement in the heat regulatory apparatus

Furthermore, experience reveals that men conditioned to a hot, dry environment did well in a "jungle" environment where temperatures were 32° C (90° F) dry bulb and 31° C (88° F) wet bulb The ability to adjust more quickly and efficiently to a hot environment after acclimatization decreases gradually over a period of weeks when subjects are removed to a cooler environment (Henschel, Taylor, and Keys 1943) Cases of heatstroke reported among industrial workers disclosed that the majority had been idle for some days before the attacks and hence could have lost some of their ability to dissipate heat (Talbott et al 1937)

Another point of practical significance is that while acclimatization results in a lowered concentration of salt in sweat the concentration is roughly proportionate to the rate of production and hence to the degree of physical exertion (Dill, 1938)

The importance of an adequate salt intake in adjusting to heat stress has been emphasized (Taylor et al 1943) Observations were made on a group of men at rest and at work in environmental temperatures of 48 5° C (120° F) dry bulb and 29° C (85° F) wet bulb during the days and 29° to 35° C (85° to 95° F) dry bulb and 18° to 24° C (65° to 75° F) wet bulb during the nights Fluids were given freely but the total daily salt intake was held at an average of 6 Gm per man for one group 15 Gm for a second group and 30 Gm for a third group The men on the low salt intake showed higher pulse rates, higher rectal temperatures at work and poorer postural cardiovascular adjustments, they lost more than twice as much body weight, drank less water and sweated less than the men on moderate salt intake Heat exhaustion and prostration with nausea, vomiting tachycardia hypotension vertigo dehydration, and collapse occurred in 25 per cent of the "low salt" group and in only 2 5 per cent of the "moderate salt" group Rest (in the heat) food salt, and water sufficed to restore all cases of collapse There was no obvious advantage gained by the group who were given 30 Gm of salt a day It was concluded that heat exhaustion and the ability to work in the heat are dependent almost wholly on cardiovascular efficiency which in turn depends upon an adequate salt intake

THE PHYSIOLOGIC EFFECTS OF SUNLIGHT ON MAN

Numerous beneficial and deleterious effects have been claimed from the direct action of sunlight upon man Sunlight is frequently included in the treatment of bone and joint tuberculosis, certain types of skin disease and rickets To the rays of the sun are frequently attributed certain tonic and stimulating properties, aside from the mere heating effects produced On the other hand, many claim that tropical sunlight in some areas has an evil influence, especially at midday, and protective coverings such as sun helmets, spine pads (Manson Bahr, 1943) and orange red underwear (Phalen, 1910) have been suggested

minute Internal and skin temperatures rise, but because the greatest increase is internal, the thermal gradient from deep tissues to skin surface is larger This favors heat loss through radiation, conduction, and convection, provided the environment is cooler than the skin surface Sweating increases the amount of surface water available for vaporization and as much as a liter per hour may be lost during work at high temperatures, representing a cooling of 580 calories As environmental temperatures equal or exceed the body surface temperature, heat loss by other means than vaporization may become negligible and heat gains may result Therefore, the amount of water vapor in the air, the relative humidity, or the wet bulb temperature becomes the most important factor in heat loss at high environmental temperatures If no vaporization can take place because the environment is saturated with water vapor, the last remaining mechanism for dissipating heat is lost and there is a complete breakdown of temperature regulation This condition results in hyperthermia which is fatal if unchecked

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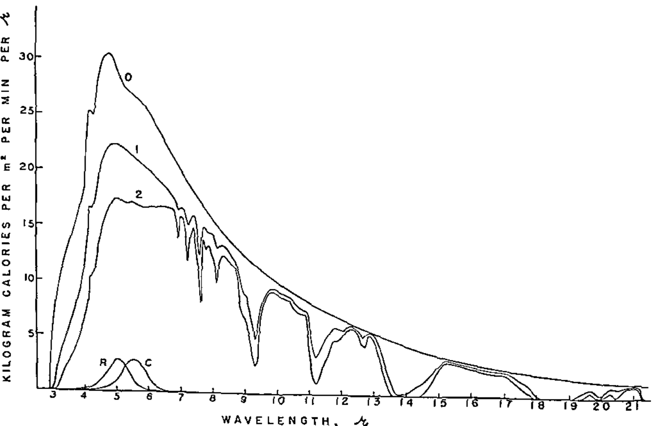


Fig. 458.—Spectral distribution of sunlight: 0, outside the atmosphere (air mass 0); 1, with sun at zenith (air mass 1); 2, with the sun at 60° from zenith (air mass 2). Curves 1 and 2 are for 20 mm. H_2O, 2.8 mm. ozone, and 300 dust particles per cubic centimeter. (From Blum, H. F.: 1945. Reprinted from Physiological Reviews with permission of author and publisher.)

A complete review of effects of sunlight which presents the most up to date information has been written by Blum (1945) The maximum intensity of the solar spectrum just outside the earth s atmosphere is at wave length 0 48 μ the wave lengths ranging from about 0 3 μ to more than 2 1 μ Sun light is arbitrarily divided into three spectral regions the ultraviolet or short waves of less than 0 4 μ the visible waves of 0 4 μ to 0 7 μ and the infra red or long waves of more than 0 7 μ The spectrum of sunlight is modified in passing through the atmosphere to the earth s surface because some wave lengths are scattered and absorbed more than others The modification is proportional to the distance traveled through atmosphere i e to the angle of the sun with the zenith The principal absorbers of sunlight are ozone which removes the shorter ultraviolet wave lengths and water vapor which absorbs the longer infrared wave lengths To a lesser extent dust smoke particles and water droplets are absorbers The scattering effects of gas molecules smoke par ticles dust and water droplets are most marked in the shorter wave lengths Many of the scattered short waves may be reflected to the earth and sunburn may occur from sky radiation even though the sky is overcast

The physiologic effects of sun s rays are dependent upon the wave length the amount of radiation reaching the body surface and the amount of reflec tion scattering absorption and penetration The wave length and intensity of radiation vary with latitude altitude time of day and atmospheric con ditions *In general solar radiation becomes less intense with increasing* latitude although the noonday summer sun at high latitudes may give more intense radiation than the noonday sun in the Tropics Reflection of sun's rays from the skin surface varies with the amount of pigment blonds reflect more light than do brunettes and Negroes as shown in Table XXXI

TABLE XXXI REFLECTION OF TOTAL SUNLIGHT BY HUMAN SKIN
(From Blum 1945)

TYPE OF SKIN	PER CENT REFLECTION
Average blond	43
Dark brunette	*35*
Dark partly Negro	30
Hindu	22
Negro	16

There is no doubt that the major portion of unreflected sunlight is ab sorbed before it penetrates more than a few millimeters and the rays with wave lengths which produce sunburn penetrate only a fraction of a milli meter Short waves about 0 28 μ are scattered in all directions by the outer corneal layers and there is therefore much absorption little reflection and little penetration A large fraction of the waves about 0 5 μ in the visible part of the spectrum is reflected from the skin and another large fraction penetrates into the corneum where it is absorbed to a great extent by the hemo globin of the blood There is little scattering of the longer waves, about 3 0 μ which are largely absorbed by the corneum

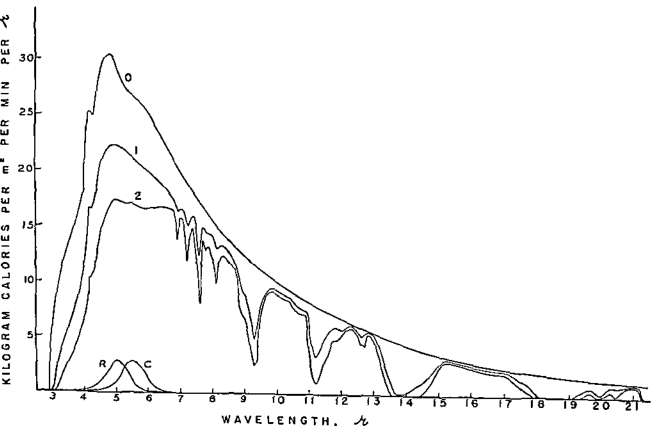


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A complete review of effects of sunlight which presents the most up to date information has been written by Blum (1945) The maximum intensity of the solar spectrum just outside the earth's atmosphere is at wave length 0.48 μ the wave lengths ranging from about 0.3 μ to more than 2.1 μ Sun light is arbitrarily divided into three spectral regions the ultraviolet or short waves of less than 0.4 μ the visible waves of 0.4 μ to 0.7 μ and the infra red or long waves of more than 0.7 μ The spectrum of sunlight is modified in passing through the atmosphere to the earth's surface because some wave lengths are scattered and absorbed more than others The modification is proportional to the distance traveled through atmosphere i e to the angle of the sun with the zenith The principal absorbers of sunlight are ozone which removes the *shorter ultraviolet wave lengths and water vapor which absorbs the longer* infrared wave lengths To a lesser extent dust smoke particles and water droplets are absorbers The scattering effects of gas molecules smoke particles dust and water droplets are most marked in the shorter wave lengths Many of the scattered short waves may be reflected to the earth and sunburn may occur from sky radiation even though the sky is overcast

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There is no doubt that the major portion of unreflected sunlight is absorbed before it penetrates more than a few millimeters and the rays with wave lengths which produce sunburn penetrate only a fraction of a millimeter Short waves about 0.28 μ are scattered in all directions by the outer corneal layers and there is therefore much absorption little reflection and little penetration A large fraction of the waves about 0.5 μ in the visible part of the spectrum is reflected from the skin and another large fraction penetrates into the corneum where it is absorbed to a great extent by the hemoglobin of the blood There is little scattering of the longer waves about 3.0 μ which are largely absorbed by the corneum

Direct physiologic effects of sunlight on the body must be limited to local changes in the surface organs such as the skin and the eye The results of sunlight on skin are the heating effect and certain photochemical reactions resulting in sunburn The heating effect is due to absorption of radiant energy with an increase in surface temperature which is usually of only a minor degree because of radiation of heat waves conduction to deeper tissues and the cooling effect of vaporization

Sunburn—Sunburn results *from exposure to the ultraviolet portion of* the spectrum which causes injury to the *unconjugated proteins or to the nucleic acids* or both of the tissue cells Some substance or substances are produced which cause vasodilatation of peripheral capillaries which after a latent period is shown by erythema In addition to vasodilatation there is an increase in capillary permeability and tissue edema with obvious swelling results A few days after the exposure at the time suntan appears there is a migration of melanin from the basal to the more superficial layer of the epidermis Later more pigment is formed in the basal layer and pre formed pigment may become darkened through a chemical change A certain amount of immunity to sunburn is acquired chiefly through thickening of the corneum and not through increased pigmentation although there can be little doubt that the erythema threshold is higher in dark than in light skins Protection from sunburn may be afforded by any substance such as glass and some plastics capable of absorbing radiation between 0 29 μ and 0 32 μ Various ointments and sunburn oils may have some influence but they vary widely in their effectiveness There are of course degrees in the severity of sunburn depending upon many factors including individual susceptibility the intensity and duration of exposure and the relative amounts of the burning rays that reach the skin When a large part of the body surface has been sunburned severe illness may result However severe sunburn may develop in temperate zones as well as in the Tropics for at high latitudes at midday the sunburn producing component of sky radiation is much greater relative to the total radiation coming from the sun than it is at low latitudes

Other effects of the sun on the skin in addition to sunburn must be considered There is growing evidence that sunlight is a major cause of skin cancer and it has been shown very clearly that skin cancer among the white population in the United States is most common in regions with the most sunlight (Dorn 1944) It is known that intensities of ultraviolet radiation below a certain critical value have relatively little carcinogenic effect and that the time between exposures is an important factor in tumor induction Rest periods permit partial recovery from the carcinogenic effects and because with increasing latitude there are fewer days during the year when the intensity of the radiation is above the critical level the carcinogenic potential is lower

Vitamin D is formed by the action of ultraviolet radiation upon some precursor steroid compound probably near the surface of the skin in the layers of the corneum Blum (1945) stated that this action is the one clear cut beneficial effect known to be produced by sunlight acting on the human skin

Some "photosensitive" individuals are unduly susceptible to a certain part of the solar spectrum. Some react with only severe sunburn while others develop variable types of skin eruptions. In addition the introduction of a wide variety of chemical substances into tissues may sensitize them to light and subsequent exposure may result in tissue destruction. This photodynamic action is one of the characteristics of the porphyrin pigments and some other substances.

Photophthalmia.—In the eye little scattering of sunlight occurs in the superficial layers and the penetration is much deeper as compared to the skin. Waves shorter than 0.32 μ are probably largely absorbed by the cornea and conjunctiva although there may be some penetration as far as the epithelium of the lens. Penetration to the retina progressively increases to a maximum at wave length 0.8 μ and falls to zero at about 1.4 μ but about one half of the energy of sunlight which reaches the retina lies in the visible and about one half in the infrared portion of the spectrum.

Sunburn of the eye, photophthalmia, may result from injury to the cells of the cornea and conjunctiva by ultraviolet radiation from direct or reflected sunrays or exposure to artificial sources of radiation. This is characterized by pain, photophobia, increased secretion, edema and purulent discharge and at times visual disturbances, the severity depending upon the intensity of exposure.

"Eclipse blindness" or scotoma following exposure to direct solar radiation is doubtless due to heat generated in the retina at the point where the sun's image is focused. However, since only about 20 per cent less light reaches the retina with the sun at 60° from the horizon than with the sun at the zenith, there is little reason for a higher incidence from this cause in the Tropics than in the higher latitudes. Looking directly at the sun is dangerous at any latitude but especially so at low latitudes where greater intensity of both direct and reflected light, especially on sandy beaches, deserts or at high altitudes, may so alter the retina as to cause visual changes.

Injury to the lens from the intense infrared radiation from glass blowers' furnaces is believed to be a cause of cataracts. Sunlight, in contrast to radiation from the furnaces, contains ultraviolet radiation which might conceivably reach the lens in sufficient intensity to damage the epithelium or the vitreous body. However, the high incidence of senile cataract said to occur in the Tropics is probably not due primarily to the high degree of insolation and other explanations must be sought. Possible nutritional and racial factors play a part.

Pterygia are known to be more common in tropical areas than elsewhere but the reasons for this are not clear. It may be that injury to the conjunctiva from ultraviolet radiation is a factor, but irritation from dust and wind may play a part and nutritional factors must not be discounted.

Proved systemic effects of exposure to sunlight are few and are practically limited to those resulting from the increased heat load or from toxic substances produced in cases of severe sunburn, and to the metabolic influence

of vitamin D synthesis Therapeutic action of sunlight claimed in a variety of conditions and usually attributed to ultraviolet radiation of wave lengths shorter than 0 32 μ has not been proved except in the case of rickets and possibly in lupus vulgaris and certain other skin conditions Sun bathing which gives a pleasurable sensation of warmth is usually associated with other influences such as rest relaxation and a pleasant environment and there is no evidence that under such conditions the sunrays in themselves have any part in the apparent beneficial effects

The solar heat load however, may be an important factor in producing systemic changes A part of solar radiation striking the body is reflected by the skin or clothing and the remainder is absorbed The absorbed portion is composed of direct radiation from the sun reflected radiation from the sky and from the soil and these separate components vary with the position of the sun and the position of the body as well as with other factors Table XXXII from Blum (1945a) shows that the total solar heat load may be nearly 4 kg cals/min for a man in the erect position with the sun at the zenith or at 60° from the zenith With the sun at an angle there is more direct and less reflected radiation of the erect figure than when the sun is in the zenith so that the total radiation is about equally distributed In the prone position however when the sun is in the zenith there is more radiation both direct and reflected than when the sun is at an angle hence the total effect is much greater with the sun in the zenith The total solar heat load may amount to 240 kg cals/hr or 1 or 3 times the resting metabolic heat load This added heat may be enough to burden seriously the temperature regulating mechanisms especially if the environmental temperature is high and the person is working Vasomotor instability vasodilatation increased pulse sweating rise in body temperature and other heat effects observed in experiments in the heat chamber may result

TABLE XXXII ESTIMATED SOLAR HEAT LOAD
(From Blum 1945a)

POSITION OF MAN	ZENITH ANGLE OF SUN	TOTAL SOLAR HEAT LOAD (KG CALS/MIN)
Erect	0°	3 87
	60°	3 86
Prone	0°	5 73
	60°	2 29

In sunburn there are photochemical changes in the superficial cells with the elaboration of substances which may be toxic Fever is frequently present in severe sunburn and may develop several hours after exposure when effects of the added heat load have been dissipated The fever is doubtless the result of toxic substances produced by cell injury from radiation The erythema of sunburn represents increased peripheral circulation which if added to the need for increased circulation for heat regulation might be a sufficient demand on the heart as to exceed its capacity In other words men with sunburn erythema have less reserve capacity to adjust to heat than men without sunburn

Since the sunrays penetrate only a few millimeters into the human skin and the superficial heat which is generated is quickly dissipated by the circulation and other means it is inconceivable that sunrays can have any direct effect on the brain or spinal cord Radiation on the top of the head has no more effect than radiation of equal intensity on the same skin area in another part of the body except possibly that a bald headed man may develop an extremely uncomfortable sunburn The effects are practically limited to increased heat load and sunburn

PHYSIOLOGIC VARIATIONS IN HOT CLIMATES

Certain physiologic measurements of tropical residents appear to differ from those of residents of temperate and cold regions However since normal values may differ with environment deviations encountered in hot climates may be beneficial rather than the reverse Adaptation usually is purposive to enable man to meet more efficiently the demands placed upon him by changing surroundings Although much has been written about man s biologic measurements in hot as contrasted to colder climates there are only a few definite clear cut differences which stand out Too often comparisons have been made between colored races in tropical surroundings and white races in the north or between relatively small and selected groups of whites in the Tropics and much larger and more heterogeneous white populations in temperate surroundings In only a few instances have the same individuals been studied over long periods in both types of climate but certain differences resulting from altered environmental influences chiefly climatic are suggested

Basal Metabolism—Basal metabolism is lower in hot climates The difference is not great but the consistency of findings warrants this conclusion A group of Europeans was studied by MacGregor and Loh (1941) for varying periods up to 2½ years after their arrival in Singapore The metabolic rate was 5 to 6 per cent below the accepted standards for temperate climates after 2½ years sojourn with apparently a gradual decline during the first year after which there was little change Martin (1930) showed how his own resting metabolism decreased from approximately 60 to 55 kg cals/hr as ambient temperatures increased during a sea voyage from England through the Indian Ocean and then as cooler weather in the Southern Hemisphere was encountered his metabolism increased again to the former level Mason (1940) who studied a group of English and American women in a hot climate reported that average metabolic rates were lower than they had been in the same women in temperate climates although there was much variation

It is probably true however that when metabolism determinations are made in the Tropics the environmental temperature is usually higher than in temperate zones Differences may be as great as 8° to 10° C Referring again to calorimetric studies (Hardy and Soderstrom 1938) it is to be remembered that heat loss from the nude body is approximately equal to heat production only within the narrow temperature range from 29° to 32° C (85° F to 90°

F.), and at higher and lower temperatures heat loss is greater than heat production. Increased heat loss at colder temperatures stimulated greater heat production and, therefore, a higher metabolism. It is probable that metabolic determinations in temperate zones are commonly made when environmental temperatures are considerably below the neutral zone, while those in the Tropics are more apt to be determined in the neutral zone. It is obvious that the conditions under which observations are made may be responsible for recorded variations and there may be no fundamental difference in metabolic rates. However, since metabolism takes place at a lower rate in warm surroundings (29° C. to 32° C.) than at cooler temperatures, there is less heat to be dissipated, and this may be advantageous.

Blood Pressure.—Much has been written on the subject of blood pressure in tropical climates. The accepted view is that both systolic and diastolic pressures average lower than in colder climates. There is an important racial factor which must be considered, for Negroes as a group are much more subject to hypertension than the white races. It was shown (Saunders and Bancroft, 1942) that, in Virgin Island Negroes, not only hypertension but also very low systolic pressures were common. Racial and unexplained nutritional factors were advanced as the causes of higher than "normal" blood pressures, and climatic factors as the reason for lower pressures. Mason (1940) and Roddis and Cooper (1926) found that blood pressures in white subjects were from 5 to 10 mm. Hg lower in the Tropics than they had been in temperate climate. Phalen (1910) showed in a group of American soldiers in the Philippines, that there was a fall in systolic blood pressure during the hot season of the year. Systolic pressures averaged about 124 mm. Hg in December and January (the cooler months) but the average dropped to 118 mm. Hg during August (a hot month).

Doubtless, it is true that, in the same individuals, blood pressure readings will average lower in a hot than in a cold environment. The logical physiologic explanation for this is the peripheral vasodilatation which develops in hot surroundings to enhance heat loss. The factor of dehydration with slightly diminished blood volume might play a small part in exceptional cases where there has been profuse sweating without adequate fluid intake. Possibly the slower tempo of life, which often occurs in tropical regions, may favor both mental and physical relaxation and play a part in lower blood pressure.

Pulse Rate.—The pulse rate under basal conditions is probably affected little if at all by residence in hot climates. Under conditions of excessive heat stress, we have seen that the pulse rate increases to speed up circulation, to aid in heat loss, and rates measured at such a time would naturally be higher. Strong (1943) cited references some of which suggested higher pulse rates in the Tropics, some lower rates, and some unchanged. The data of MacGregor and Loh (1941) suggest that pulse rates are lower in Europeans living in Singapore than would be expected in a temperate climate, but his subjects were military men who had undergone months of physical training and might be expected, therefore, to have slower resting rates. Mason (1940) also noted

slower pulse rates in English and American women after a period of residence in India Considering available evidence it seems warranted to conclude that there is a slight slowing of the resting pulse rate in the Tropics probably commensurate with the slight decrease in metabolism, but that physical exertion will cause a greater increase in rate than would be expected in cold climates, because of the added heat stress

Body Temperature—There is essentially no difference in resting body temperature in the Tropics as compared to other regions, but a greater increase with exercise may occur in the Tropics especially in unacclimatized persons, due to the added heat burden Brennemann (1943) showed that, in healthy children and in adults in temperate climates, a rectal temperature of 38° C (101° F) after exercise was a common finding even though the mouth temperature was normal Taylor et al (1943) stated that work in the heat increased body temperatures by 1 7° C (3° F) in unacclimatized persons, while the increase was only 0 8° C (1 4° F) after a period of acclimatization Skin temperatures may be slightly elevated (Sundstroem, 1927) but this is dependent upon environmental temperatures and relative humidity

Urinary Output—The urinary output is ordinarily much less in hot than in cold weather, and the daily volume of urine will normally be considerably less in the Tropics than elsewhere because of increased amounts of water loss in perspiration With decreased output of urine the specific gravity is usually high because of the greater concentration of solids but in case of excessive sweating with inadequate salt intake chlorides may entirely disappear from the urine (Dill, 1938)

Menarche—There is still much confusion regarding the age of onset of menstruation especially in reference to tropical residents and widely divergent statements are made Manson Bahr (1943) stated "In children, puberty is attained at an earlier age so that in European girls menstruation commences about a year earlier than in temperate climates"

Mills (1942) however on the basis of his own observations believes that the onset of the menses is delayed in the Tropics about a year or more Factors other than mere climate and place of residence influence the time of onset of menses such as heredity and the social and economic status of the subjects In a study made among Filipinos by Bersamin and Gonzales Bersamin (1940), it was shown that there was little difference in the age of menarche of women living in a cool mountain province (13 41 years) and in those living in hot, humid lowlands (13 88 years) There was more difference between women of higher and lower social status, the onset averaging 13 31 years for the former and 14 35 for the latter

Bland (1932) has presented what is probably the most logical and credible attitude toward this question He states that climate has practically no influence, race very little, and that surroundings education, and nerve stimulation stand out prominently as the factors which determine the advent of

puberty He states Today it is believed that the age of the first menstrual period except for slight variations, is nearly the same in all parts of the world "

Psychologic Reactions to Tropical Environment—The term 'tropical neurasthenia" has been used for years in many standard texts on tropical medicine to indicate a condition which was allegedly the result of residence in tropical regions The condition characterized by bizarre and manifold symptoms of nervous irritability, fits of sudden anger despondency excessive indulgence in alcohol or sex careless work feeling of weakness and malaise 'spots before the eyes " etc has frequently been ascribed to the tropical environment especially to the heat and humidity if in a jungle area the dryness if in a desert region and to tropical sunlight McCartney (1944) stated that "where there is continuous heat with no winter, white men do not last long even if they escape infections " and he further stated that among American missionaries the majority of whom had been in tropical countries about 36 per cent were furloughed home because of neuropsychiatric problems One wonders if the same proportion of neuropsychiatric problems would not have appeared had the same individuals remained at home in a temperate climate but subjected to for them unusual psychic stress

It is well known that large population groups descendants of the British in the West Indies and elsewhere of the Portuguese and Spanish in Latin America many of them of European racial strain unmixed with colored racial strains, have lived successfully for generations in hot countries without showing any undue increase in psychiatric problems Man whether European Asiatic Central African or Caribbean frequently reacts against mental trauma and stress with a variety of abnormal behavior patterns whether at home or abroad whether in the Arctic or the Tropics The type and severity of reaction will depend much upon the total personality make up the sum total of his experience and the character and severity of the psychic stress

It is true that the temporary resident of the Tropics in many cases is afflicted by undeniably noxious stimuli such as fear and anxiety of disease insect pests loneliness frustration and annoyance at the slowness of ' native" groups (Stannus 1926 1927) But in most cases the maladjustment is sociologic rather than physiologic We agree with Culpin (1933) that there is no neurasthenia" peculiar to the Tropics There are however many instances where unstable personalities are incapable of carrying on a normal life in the strange new and often unfriendly tropical environment Frequently, too the added burden of malaria intestinal parasites and possibly malnutrition from an inadequate diet consisting of canned foods may tip the psychic balance to the abnormal

Hill (1943) supports the view that there is no real evidence that tropical climate is the chief cause of "tropical neurasthenia " and he states ' there is no state of neurasthenia due purely to the effect of tropical climate on a previously healthy person " In a study made of 500 admissions to a tropical hospital among 50 patients showing neurasthenic or neurotic states most of them

had personality difficulties or latent neuroses existing before tropical experience In some the effects of organic disease appeared to predispose to breakdown

'Tropical neurasthenia then may be concluded to be a figment of the imagination It is true that neurasthenic states may develop more often among temporary tropical residents than among a comparable group in their indigenous environment but the cause is not climate but a variety of complex factors acting upon an unstable personality

Heat Sickness—One cannot leave the topic of physiologic changes in hot climates without a brief discussion of acute illness resulting directly from excessive heat loads A vague and indefinite nomenclature has developed to label the resulting conditions for example heat cramps stoker s cramps heat exhaustion heat stroke heat pyrexia thermic fever and sunstroke

In spite of the number of names the acute effects of heat fall into only two classes The first is characterized by cramping pains in skeletal muscles and in the abdomen with or without nausea and vomiting It is associated with lowering of blood chlorides and hemoconcentration resulting from the excessive loss of salt with perspiration and there may be a coincident increase in body temperature and pulse rate This condition of heat cramps is common in workmen who are laboring under great heat stress as occurs in steel mills stoke holds and deep mines Commonly such cases occur with greater frequency during the first few days of a spell of hot weather and among men who have returned to their jobs after an absence of a few days In such circumstances the adaptation to heat has not yet been gained or was partially lost as in the case of the absentees as stated above

The second type of acute illness presents a variety of symptoms nearly all resulting from failure of the circulation or of the heat regulating mechanism or both The total heat load from hot environmental temperatures direct sunlight and physical exertion has become so great that heat accumulates in the body The underlying physiology has already been discussed in some detail The result is increased body temperature which may exceed 41° C (106° F) in which case the prognosis is grave rapid pulse unstable blood pressure a generalized feeling of weakness and exhaustion and faintness in some cases Stupor or unconsciousness may follow even in the horizontal position and in such cases perspiration usually stops for lack of adequate circulation There may be associated nausea and vomiting with further loss of chlorides In certain cases there is little if any increase in body temperatures and the outstanding symptoms are faintness and weakness due to circulatory failure This second type of acute illness should probably be called heat prostration or heat pyrexia depending upon the salient signs and symptoms

The usual treatment of heat cramps is administration of water and salt with or without glucose and rest in a cool place Two Gm of sodium chloride and 4 Gm of dextrose in 200 c c of water may be given by mouth every 15 to 30 minutes until symptoms have subsided Rarely is intravenous infusion of saline necessary

As a preventive measure workers in excessive heat should take 1 or 2 salt tablets each containing 0 5 Gm sodium chloride with water several times during the day In some localities it is customary to provide drinking water containing 0 1 per cent sodium chloride

Treatment of heat exhaustion or heat pyrexia consists of removal to a cool environment if possible and the administration of salt and water by mouth or parenterally If pyrexia is a prominent feature the body should be cooled by spraying with cold water or alcohol or by wrapping a wet sheet and exposing to a breeze Ice enemas or ice packs may be necessary but must be used cautiously for the sudden shock of cold may cause death due to complete circulatory collapse

The geographic distribution of heat sickness is not well identified due to vague terminology and the great variation in reporting cases and deaths Reports available give a definite impression that deaths from heat are more numerous in temperate than in tropical climates There is a rational explanation for this inconsistency We have seen that adaptation to heat develops within a few days or weeks and is lost slowly over a period of weeks in a colder environment Inhabitants of temperate climates lose their adaptation during cool weather and are thus unprepared to meet sudden spells of heat efficiently On the other hand in the Tropics where temperatures are consistently high without much seasonal variation adaptation is not lost Apparently deaths from heat in the Tropics occur more often in persons of European than of native races although the latter are by no means immune Europeans are more apt to be poorly adapted to heat because of recent arrival and in general they do not learn to adjust their habits and clothing to minimize heat load as well as the indigenous races (Collings 1942 Brown 1935 Shattuck and Hilferty 1936 Dreosti 1934)

SPECIAL FEATURES OF THE TROPICS

In addition to reactions to heat and to the underlying physiologic mechanisms there are other important factors peculiar to a tropical environment The flora and fauna are different in the Tropics and at times may contain elements dangerous to health and life Many diseases seldom found elsewhere are prevalent in the Tropics The noxious flora and fauna and specific diseases are mentioned briefly here because of their important bearing on tropical hygiene

Tropical Flora —Many plants peculiar to the tropics are injurious to man Some may cause poisoning when ingested while others are tropical contact irritants Examples of the former are the akee *(Blighia sapida)* commonly used for food on some islands of the West Indies and the fruit of the manchineel tree *(Hippomane mancinella)* which is also common in the Caribbean area and may be eaten by the unwary Examples of the latter are iroko allergy and sensitivity to the manchineel and the ordinary mango The wood of the African teak may cause severe contact dermatitis Many other plants extracts of which are used medicinally are common to the damp tropical regions

and ingestion may lead to severe poisoning. It is important not to eat unfamiliar fruits or plants in the Tropics unless assured they are perfectly safe.*

Tropical Fauna.—Insects, spiders, scorpions, reptiles, fish, and other forms of animal life which abound in many tropical regions may be simply pestiferous, or they may constitute a danger because of poisonous bites or stings, or may be the means of disease transmission. In some jungle areas the ravenous biting of many species of insects and the itching or painful reaction to the bites may make life unbearable. Mosquitoes and insects of the genera Culicoides, Simulium, and Phlebotomus, may be troublesome pests as well as vectors of disease. Poisonous snakes may constitute a real hazard in some tropical areas; the cobra in India, the black mamba of West Africa, and the rattlesnake of interior Brazil are well known examples. Some fish are poisonous when eaten; other species have poisonous stings; and the mutilating bites of the barracuda and of the piranha of the Amazon Basin may be fatal.

Diseases of the Tropics.—Tropical residents suffer from nearly all the illnesses which are common in temperate and cold zones, and in addition there are many diseases which are common in tropical areas but rare elsewhere. There are some conditions, notably rheumatoid arthritis, rheumatic fever, rheumatic heart disease, and clinical diphtheria, which are relatively uncommon in hot countries.

There are few diseases which are strictly limited in their distribution to warm climates, and in most instances these are restricted because the vector or vectors necessary for transmission require a minimum temperature for their survival and multiplication. Malaria, although it is endemic in many non-tropical areas, is far more common in the Tropics and subtropics where it assumes tremendous importance in many regions and is one of the prime causes of morbidity and mortality. The distribution of malaria is determined largely by climatic conditions favorable to the survival of the anopheline vector. Yellow fever, although it was once epidemic along the Atlantic coast of the United States, and in Europe, is now confined to tropical areas in South America and Africa (Scott, 1939). The mosquito vectors of this disease, however, have a much wider distribution than the disease and are found in many areas of the temperate zones. The disappearance of yellow fever from the southern United States and the Caribbean area, while the mosquito vector persisted, suggests that factors other than the presence of suitable vectors are necessary for the disease to propagate. Yaws is one outstanding example of a disease which is strictly tropical in its distribution, for it is endemic only in hot, relatively wet areas. The reasons for the limited distribution are not clear. It may be that warm, moist climatic conditions favor the development of florid, open lesions of yaws, which are the sources of infection for other persons, or that an insect vector is involved which is limited in its distribution by climatic factors (Saunders et al., 1936). Diarrhea and enteritis caused by pathogenic organisms are widespread throughout the world, but they are

* An excellent discussion of this subject may be found in the handbook issued by the U. S. Navy, *How to Survive on Land and Sea.*

most prevalent where local conditions permit the pollution of food and water with human feces These conditions are encountered most frequently in tropical areas due largely to social and economic factors and it is not surprising that intestinal diseases reach their highest prevalence in the Tropics and Subtropics Although lack of adequate environmental sanitation is largely responsible climatic factors also play a part Heat and moisture are favorable to the survival and multiplication of pathogenic organisms outside the body especially in contaminated food

There are other diseases which have greater prevalence in some parts of the Tropics and Subtropics not because of the direct effects of climatic conditions but because of the generally low social and economic level Leprosy for example which was once common in northern and central Europe as well as elsewhere has almost disappeared from the cold countries of Europe and the areas of its greatest prevalence are now the Tropics and Subtropics The distribution of the disease has varied with changing conditions the highest incidence generally coincides with areas of poor social economic and hygienic conditions (Saunders 1942) Poverty unsanitary surroundings ignorance and malnutrition foster the propagation of most communicable diseases and probably have a great deal to do with the present prevalence of leprosy yaws and other diseases in certain areas

PRACTICAL POINTS ON INDIVIDUAL HYGIENE

The added heat burden and the greater risk of infectious diseases are the two main factors to be considered in connection with life in the Tropics Man s physiologic reactions to heat and the mechanism of his adjustment and adaptation indicate that some positive actions can be taken which will contribute to make life in the Tropics healthy and comfortable Furthermore certain simple prophylactic measures in addition to community sanitation can be taken by the individual to avoid infectious disease

The extra heat load imposed in the Tropics can be minimized by proper habits of life and work and by proper food clothing and housing The habits of life and work are important The tempo of activity should be slowed down If it is necessary to walk outside in the heat of the day a leisurely pace should be the rule to avoid excessive sweating with its attendant discomfort and loss of chlorides and fluids On the other hand regular physical exercise is important to keep fit in the Tropics probably more so than in colder climates as heat dissipation by the body depends largely on an efficient circulatory system which is dependent in part upon exercise Various outdoor sports or walking in the cool hours of the day should be encouraged both for their physical effects and for their entertainment value However exercise should not be taken to the point of exhaustion and undisturbed rest and sleep are essential for good health although there is no reason to suppose this is truer in the Tropics than elsewhere

Price (1939) has stressed the importance of physical work in maintaining health in the Tropics It has been demonstrated time and again that northern

whites can do hard labor in the hot wet or hot dry Tropics probably as efficiently and well as dark skinned races and maintain good health The North American laborers who had so much to do with building and maintenance of the Panama Canal and the American and European labor battalions in World War II are good examples

In the Tropics entertainment is essential for the idle hours and this is especially true of isolated stations where the dull monotony of days and nights of sameness may be an important factor in activating latent neuroses or in driving a person to drink Outdoor games are beneficial physically as well as mentally There are few places where enough players cannot be assembled for some type of game and tennis golf cricket and baseball are all popular in many tropical communities Fishing or hunting may afford welcome relaxation During recent years few places are so remote as not to be reached by radio and the movies Photography is a fascinating hobby and diversion and has helped many a man in an isolated bush station

Alcohol—There are probably few races or times in history when fermented beverages were not part of the daily life or religious ritual Someone once said that alcohol is a beneficent mistress and should not be abused This is true in any part of the world regardless of geography or climate and the intemperate use of alcohol should be avoided In many parts of the Tropics the custom of the sundowner is observed a cold alcoholic drink after the day s work is finished Individuals and races will differ in their drinking habits but alcohol may be beneficial to those who are accustomed to *a drink or two before the evening meal because of the social implications* and the mild stimulation of the appetite The quart a day men are more apt to come to grief in the Tropics than elsewhere however for inebriation leads to lack of care in avoiding infections Furthermore the diet already restricted in vitamins may be reduced in quantity and frank vitamin deficiencies may develop

Food—An adequate diet is necessary anywhere for the preservation of health it must provide sufficient calories at least a minimum of protein including the essential amino acids sufficient mineral salts and vitamins In addition to the nutritional requirements food should be palatable and free from pathogenic organisms and from organic or inorganic toxins or poisons Unfortunately an adequate and safe diet may be difficult to obtain in many parts of the Tropics especially in rural areas where the indigenous population is semicivilized and poverty and lack of sanitation are the rule Rice for example is the principal food throughout vast tropical areas but too often the vitamins have been largely removed by milling such a diet thus becomes deficient not only in protein but also in vitamins In other areas where maize or taro provides the bulk of the available food there is a similar lack as a result deficiency diseases particularly those caused by a lack of adequate supplies of vitamin A and factors belonging to the B complex group are relatively common throughout much of the Tropics There is an increased prevalence of night blindness scaling and hyperkeratosis of the skin keratitis neuritis nutritional edema and pellagra

A physically active adult will require 3 000 or more calories of food value each day of which *the protein constituents should probably* be about 1 0 Gm for each kilogram of body weight However, since protein stimulates metabolism it is advisable in the Tropics to keep the protein consumption low to minimize the heat burden and the greater part of the caloric intake should be in the form of carbohydrates Because animal proteins meat and fish are often scarce in tropical areas and milk is seldom available in sufficient quantities much of the protein supply must come from such plant sources as rice and beans However grains and legumes are often deficient in some of the essential amino acids particularly cystine and must be supplemented by some form of animal protein (McLester 1940)

Adequate vitamin intake can usually be assured by careful attention to the diet *Vitamin A is present as the carotene precursors in substantial* amounts in green leafy vegetables such as broccoli spinach and chard in ' yellow ' fruits such as avocados apricots mangoes bananas and plantains *in egg yolk and mammalian and fish livers* Edible greens can be grown almost anywhere and this together with fruits mentioned should furnish adequate amounts of fat soluble vitamin A Whole milk and butter fat are also potent sources of vitamin A and should be consumed when available Supplementary vitamin A can be supplied in large amounts but in small bulk by the various commercial fish liver oils

Vitamins of the B complex group especially thiamin chloride riboflavin and nicotinic acid are often deficient in quantity among rice eating peoples due to the custom of milling and polishing the rice This processing helps to keep the grain from fermenting but removes most of the germ and outer layer of the seed and takes away much of the vitamin content Van Veen (1940 1941) *reported* that 500 Gm of husked rice contained about 400 units of vitamin B (thiamin) while the same amount of undermilled rice contained about 250 units and polished rice retained about 100 units Vedder (1943) *stated that deficiencies associated with a polished rice diet were* not usually made up by the limited amounts of fish and vegetables taken and that polished rice is deficient not only in thiamin but also in riboflavin the fat soluble vitamins A D *and E and inorganic salts especially calcium and iron*

Unpolished rice the commercial brown rice is a good source of the vitamin B complex and should be eaten in preference to the polished ' white' rice especially when there is a question of *the adequacy of vitamin supply* Whole seeds and whole grains as well as milk eggs yeast and liver are generally a good source of thiamin Fruits and vegetables although variable in their vitamin content are also important sources

Riboflavin like carotene is found in the green leaves of growing plants and also in milk eggs and liver Yeast is another potent source of riboflavin

Vitamin C ascorbic or cevitamic acid is plentiful in citrus fruits tomatoes and like carotene is found in close association with chlorophyll in the green parts of plants Fresh or canned green leafy vegetables are valu

able sources of this vitamin Generally marked vitamin C deficiencies are not common in tropical areas probably because relatively small amounts of this vitamin suffice to prevent frank scurvy Minor degrees of this deficiency may however exist

Rickets and other manifestations of vitamin D deficiency are seldom seen in the Tropics probably because there is an abundance of sunlight which causes synthesis of the vitamin in the skin Vitamin D is not found in plants but is present in fish oils milk eggs and other suitable sources

Methods of preparing foods have important effects on their vitamin content The fat soluble vitamins although relatively thermostabile are destroyed by oxidation Introduction of air by excess stirring should be avoided during cooking Water soluble vitamins tend to withstand boiling in an acid medium but are rapidly destroyed if heated in an alkaline medium The habit of adding baking soda or other salts to green vegetables ' to bring out the color should be discouraged Since water dissolves the vitamins only a small quantity of water should be used in cooking and it should not be discarded otherwise valuable water soluble substances are thrown away

A diet of whole grain cereals unpolished rice fresh fruits green leafy vegetables with the addition of relatively small amounts of fish and meat is usually adequate in calories vitamins and salt Such a diet can be secured nearly everywhere However even though the food supply may be adequate in quantity and quality the palatability and purity may leave much to be desired Care and imagination in the preparation of attractive dishes are too often sadly lacking in many localities where a monotonous diet of rice beans corn meal and perhaps a little fish now and again is the accepted standard Among many people the prejudices against fresh fruits and vegetables the ingrained eating habits food taboos etc may make it difficult to secure an attractive and adequate diet even in the presence of plenty

Dangers from gastrointestinal infections and food poisoning are ordinarily greater in the Tropics than elsewhere In most small towns and rural areas where environmental sanitation is often lacking the opportunity for the pollution of food and drink with human feces is great Furthermore the careless habits of food handlers and cooks many of whom are carriers of infective microorganisms favor contamination with enteric pathogens In some regions the custom of fertilizing with night soil is an added hazard and the relatively high environmental temperatures and the frequent absence of refrigeration favor decomposition of food and growth of bacterial infectants

Fresh fruit and vegetables should not be eaten raw under such circumstances but should be thoroughly cooked The exceptions are the fruits which can be peeled before eating in other words those which have a rind or hull are safe to eat raw if the envelope is carefully removed Washing lettuce and other greens in dilute permanganate or iodine solution is not adequate to remove or kill amebic cysts and other pathogenic organisms and should be discouraged for it gives a false sense of security Leftover foods should not

be kept for future serving because of the danger of food poisoning unless one can be assured of cleanliness in the handling of the food and prompt and adequate refrigeration

Much can be done to prevent gastrointestinal infections and food poisoning if sufficient controls are imposed upon cooks food handlers and kitchens A great deal depends upon proper selection of personnel and upon training in the elements of cleanliness Food handlers if possible should be examined by a physician to eliminate those with obvious communicable diseases Stool examination should be made to exclude carriers of parasites and other enteric pathogenic organisms When this is not feasible selection of personnel should be made after careful questioning about symptoms suggesting gastrointestinal and respiratory infections A cook or other servant who makes too frequent trips to the latrine should be relieved of his post for a time The domestic personnel kitchen facilities and storerooms should be inspected with frequent regularity and emphasis placed on clean hands clean clothes clean kitchens clean dishes and prompt disposal of garbage and refuse Great tact must be used for often a faithful servant will rebel at too much interference In some places the domestic heirarchy is such that an employer may not set foot in the servants domain or both parties will lose face

Salt—The importance of an adequate intake of sodium chloride especially where work is done in the heat has already been emphasized Men doing hard work in the heat need a minimum of probably 10 to 15 Gm of salt to replace that lost in sweat The need is greater during the first few days of exposure to heat when salt loss is greater than after a period of adaptation Salt may be taken in several ways Table salt should be used freely at meals The drinking water may have enough salt added to make a concentration of 0 1 per cent which is still palatable This is probably better than the use of salt tablets which some believe cause symptoms of gastric irritation Recently a new type of tablet has been devised (Consolazio et al 1944) which by allowing salt to be released slowly has eliminated most of the unpleasant features This is a tablet of sodium chloride 0 65 Gm impregnated with cellulose acetate or cellulose nitrate The impregnating material acts as an inert sponge which is not affected by digestive secretions and is excreted in the feces When salt tablets are used 1 or 2 should be taken each time water is drunk

Water—One of the prime essentials for life is an adequate supply of pure potable water In many tropical regions as well as elsewhere water supplies while adequate in quantity are apt to be contaminated with pathogenic organisms and should be purified before drinking A detailed discussion of water sources and purification cannot be included here but a few general remarks are indicated

The source of water must be considered in relation to its potability Many large cities in tropical areas have pure safe water supplies and adequate purification and supervision to ensure a constant safe supply Usually information concerning the water supply can be obtained easily from local health au

thorities and physicians However in many cities water from the mains is not safe for drinking without further treatment In some places where chlorination is practiced there is inadequate supervision of this process too little chlorine is added and possibly bacteriologic checks are not made carefully or frequently Sometimes raw untreated water from a polluted source is pumped directly into the mains In some cities where there is low pressure in the mains booster pumps are permitted to force water into high buildings This practice and the common custom of cutting off the pressure during certain hours of the night may lower the pressure sufficiently so that polluted ground water may force its way into the water mains and contaminate an otherwise pure supply Unless one is assured that the water supply is safe it should be assumed to be polluted and should be treated to render it potable

The simplest way to sterilize water for household use is of course by boiling A quantity sufficient for drinking purposes for a 24 hour period should be boiled for not less than 15 minutes in a covered container It is usually necessary to exercise careful supervision over the servants who may be given this detail otherwise they tend to become lax and the water is not properly sterilized

Of all the chemical substances used to purify water chlorine in some form is probably the most universally used and the most practical for example chlorine in the form of HTH (high test calcium hypochlorite) or one of the chloramines notably halazone (p sulfonedichloroamidobenzoic acid) It is agreed however that chlorination in quantities sufficient to render the water free from pathogenic bacteria is not necessarily effective in destroying the cysts of *Endamoeba histolytica* It is also to be remembered that water with much turbidity or suspended organic matter requires more chlorine than clear water Furthermore chlorine is less active in water with a high pH and more active in water that is relatively acid (Brady et al 1943 Chang 1944) Tests show that there should be not less than 0 2 p p m of residual chlorine at the end of a given contact period to ensure adequate bactericidal action The recommended dose of calcium hypochlorite is 3 77 mg per liter of water but about twice this amount 7 54 mg per liter is necessary to destroys cysts of *E histolytica* (Brady et al 1943) However if contamination with amebic cysts is suspected chlorine should not be relied upon to purify the water The high chlorine content necessary to ensure sterilization probably more than 4 p p m makes water distasteful

Halazone tablets are useful for field trips and for emergency sterilization of small amounts of water when boiling is impractical One or two tablets for 500 c c of water is the usual dose The tablets should be crushed into a powder and shaken into the water which should be allowed to stand for 30 minutes before drinking

It should be remembered that freezing has little effect on most pathogenic microorganisms When ice is used to chill beverages care should be taken that the ice has been frozen from water which meets the required standards

of purity Too often people labor under the false sense of security that ice *ipso facto* pure and while they will take great care to ensure that the wat they drink has been boiled or otherwise treated they will cool their drink with ice from unknown sources

In addition to being bacteriologically safe water must be adequate amount This is especially true when there is physical exertion in a hot e vironment Daily individual requirements under conditions of strenuou work may be as high as 30 liters as indicated in Table XXXIII

TABLE XXXIII DAILY FLUID REQUIREMENTS UNDER VARYING CONDITIONS
(Summarized From War Department Circular Letter No 119)

ACTIVITY	FLUID REQUIREMENTS IN LITERS WHEN MAXIMUM DAILY TEMPERATURE IS 95° F	105° F	115° F
Light work	4	6	10
Moderate work	5	7	11
Heavy work	[illegible]	9	13

Bath water if untreated may also be a source of danger especially i areas where schistosomiasis is prevalent Recent experiments which hav not yet been made public indicate that chlorine is effective in killing cercaria in strengths of 1 to 2 p p m Furthermore if water is allowed to stand fre *from additional sources of contamination the cercariae will die within 24 t* 48 hours

Care in laundering clothes is also an important hygienic point in th Tropics Various molds fungi and mites as well as other organisms which ma cause skin diseases may be acquired through improperly laundered clothe It is the habit of the washwomen in some places to soak clothes in contam inated stagnant water It is known that scabies and ringworm may be con tracted from freshly laundered clothing

Clothing—Fashion normally dictates the type and kind of clothing an often the results place the body at a disadvantage with respect to heat regu lation Martin (1930) wrote In my experience the obstacle to work i hot climates is for the European as much a social as a physiological one The coolie works with his nice brown body exposed and covered with swea and is jolly whereas the white man distressfully labors in a hypertherm *condition straining* his heart to work a refrigeration plant which he ha rendered inefficient because his sense of dignity forbids him to expose hi skin"

The design fabric and type of garments worn in the Tropics should hav for their chief objectives coolness and protection from sunburn excessiv *heat load and from abrasions and insect bites* In general clothing should be light in weight light in color and have as few layers as possible Covering the body raises the skin temperature with a resultant decrease in the thermal gradient and less heat evaporation The cardiac output in the nude body is estimated to be about 10 per cent higher in an environmental temperature of

38.5° C. (102° F.) than in lower temperatures. On the other hand the increase with the body clothed is more than double this amount (Wulsin 1943).

That color and weave are important factors is indicated by Table XXXIV

TABLE XXXIV. THE TRANSMISSION, REFLECTION AND ABSORPTION OF SUNLIGHT BY VARIOUS TYPES OF FABRICS

(Adapted from Wulsin, 1943)

TYPE OF FABRIC	SOLAR RADIATION, PER CENT		
	TRANSMITTED	REFLECTED	ABSORBED
8.2 ounce khaki	0.0	56	44
Cotton herringbone twill, olive drab	0.1	26	74
Cotton percale, white	0.5	67	33
Cotton percale, olive drab	2.5	48.5	49

adapted from Wulsin's figures. White reflects more and absorbs less solar radiation than colored cloth such as khaki, and some weaves, such as percale, reflect more than rougher fabrics such as herringbone twill. Therefore white smooth surfaced material is best in hot climates for minimizing the heat load which is increased by covering the skin with clothing.

Ordinarily, except when exposed to direct sunlight when the danger of sunburn may be a factor, as little of the body surface as possible should be clothed—consistent with custom and fashion. Other practical factors in connection with the design and type of clothing must be considered, such as laundry facilities. White materials are generally unsuitable for field conditions, for which the most practical and suitable material among many tested was found to be 8.2 ounce khaki cloth.

For men, loose fitting, short sleeved shirts and short trousers are probably the best type of clothing for hot climates and are customarily worn in many parts of the Tropics during the daylight hours. However, where insects are a problem and where malaria is endemic, the legs and arms must be covered to protect them from insect bites, especially after dark.

Multiple layers of clothing should be avoided for it is known that each layer presents an additional barrier to heat flow, and a single layer is ordinarily all that is necessary. Frequent laundering is essential in hot climates because light colored fabrics soil easily and the garments soon become saturated with the accumulated precipitations from secretions of the sweat glands. These, if allowed to accumulate, favor skin irritation.

There is no evidence that special protective devices such as *sun helmets*, woolen spine pads, orange red underwear, or cholera belts possess any virtues in protecting men from the effects of tropical climate. Phalen (1910) reported on an experiment carried out many years ago in the Philippines on the effects of orange red underwear. For a year he observed a group of men in orange red and a control group clad in white underwear of the same weight and texture. There was no essential difference in physiologic measurements between the two groups and the "white" group probably were a little more comfortable.

Headgear —Much has been written in the past about the deadly effects of the tropical sun on the head and neck especially in certain parts of Africa and India where it has been customary among most Europeans to persist in wearing heavy protective helmets which have projecting rims in the back to protect the neck There is no established evidence that such headgear is necessary or even advisable although residents and visitors are more comfortable when their heads are protected from the direct rays of the tropical sun It has already been pointed out that the effects of sun's rays on the head and neck are not different from the effect of sun s rays on other parts of the body and helmets simply add to the heat load in proportion to the area exposed to the sun s rays Broad brimmed lightweight headgear preferably light in color is helpful in shading the upper part of the body and in cutting down the glare particularly when the sun s rays are directly overhead Glover (1942) measured the temperatures under various types of head coverings exposed to a uniform heat source He found the temperature was lowest under a pith helmet lined with aluminum and weighing 280 Gm but the temperature under an ordinary Panama hat weighing only 110 Gm was very little higher The highest temperatures were obtained under cork helmets and felt hats

Head nets, which are merely loose bags fashioned from mosquito netting draped over the hat or helmet to reach the shoulders may be needed at times to protect the head and neck from insects

Footwear —Lightweight shoes particularly those with canvas uppers are most comfortable in hot climates However for rough terrain and for operations in rural areas heavier shoes must be worn Canvas leggings are used to protect the legs from abrasions and insect bites and are as serviceable as the heavier spiral or leather puttees

Mosquito boots are commonly worn in certain areas where malaria and other mosquito borne diseases are prevalent They are loose fitting lightweight boots usually made of white canvas or thin leather which reach to just below the knee where they are held with a tie They are ordinarily worn during the hours of darkness and not during the daytime

Sunglasses —Intense glare in the Tropics may be troublesome and also may have some physiologic effects on the retina Furthermore the ultraviolet rays may cause sunburn of the conjunctiva and the reflected longer rays may cause irritation from the heating effect Sunglasses are advisable to protect the eyes against direct and reflected sunlight These should be large enough to protect against side lighting and of a proper color to absorb the longer rays Any glass of course will absorb the ultraviolet part of the spectrum

Care of Clothing —In damp jungle areas one of the great problems is to preserve clothing from the flourishing growth of fungi and molds which appears to spring up almost overnight Shoes and woolen articles left in a closet may become covered with mold in a day or two Articles not in constant use should be thoroughly dried in direct sunlight or near a source of heat such

as the cook stove and placed in an airtight metal trunk of the type commonly used in West Africa A tight cupboard or closet should be provided for other articles and if electricity is available a light left burning in the cupboard will help keep the air dry and keep down the growth of molds

Care of the Skin—Extra skin care is necessary in most tropical areas especially in the damp jungle regions because of the prevalence of various skin diseases such as fungus scabies and other dermatitides Prickly heat which is caused by excess sweating and which in itself is annoying predisposes to secondary infections of various kinds Skin care involves frequent bathing with a bland soap after which the surface should be dried thoroughly and powdered with some form of borated talcum For prickly heat in addition to keeping the skin as dry as possible applications of 1 2 000 bichloride of mercury in 90 per cent alcohol has been found to be useful

Care of the Feet—Care of the feet is especially important Extensive fungus infections of the feet or extremities which have been called Hong Kong foot jungle rot and various other names is common in portions of the damp Tropics especially where foot hygiene is neglected Again frequent bathing with attention to drying the skin between the toes and the use of various dusting powders is important Socks should be changed daily and should be boiled and ironed if fungous infection has been acquired

Old shoes which have become contaminated with fungi may remain a source of reinfection They either should be thrown away or an attempt should be made to sterilize them To destroy fungi it has been recommended that shoes be placed in a closed container for 24 hours with a sponge soaked in formalin (Pillsbury et al 1943) Shoes treated in this way should not be worn for at least 48 hours after exposure to formalin because of the danger of developing a chemical dermatitis

Use of Insect Repellents and Insecticides *—Insect repellents of value in protecting against the annoying and sometimes dangerous bites of insects have been developed during World War II The most useful of the compounds are dimethylphthalate Rutgers 612 and Indalone

Laboratory and field tests show that these repellents vary in effectiveness against different species and may fail to repel some A mixture of the 3 preparations in the proportions of 6 parts of dimethylphthalate and 2 portions of each of the others has been found to be effective against most insects One application of the mixture usually gives good protection for several hours depending on various factors such as the amount of perspiration and type of insect involved

Clothing may be impregnated with a 5 per cent emulsion of dimethyl phthalate and garments so treated will retain their repellent properties for several weeks This is especially important when travel is necessary in areas where scrub typhus is endemic †

*See also Chapter 35

†Editor's note (O F) Benzyl benzoate and D butylphthalate have gained adherents recently for the control of mites and chiggers in such areas

The greatest advance in recent years in the use of insecticides has been the discovery of the efficacy of DDT (dichlorodiphenyl trichloroethane). The preparation is especially effective against mosquitoes both adult and larval forms, houseflies, lice and fleas. DDT has two principal advantages over other insecticides: first, it is effective in low concentration and second, it has a prolonged residual effect against *most insects*. *DDT is used in a 10 per cent* concentration as a powder with talcum, in a 5 per cent oil solution or, less frequently, as an emulsion. For the control of mosquito larvae DDT may be applied in an oily solution, in aqueous emulsion or as dust. The application of 0.1 pound of DDT to 1 acre of surface will effectively control anopheline larvae. For adult mosquitoes DDT is commonly used in an oil spray applied to the walls. This kills all adult mosquitoes which come into contact with it and the residual which is deposited on walls and other surfaces remains effective for several weeks.

Oil sprays are used in controlling house flies. The walls of the affected premises should be thoroughly sprayed with a 5 per cent solution in oil. After *one or two seasons' use, the flies in the area become resistant to DDT so that* other insecticides, as Chlordane, Lindane (γ benzene hexachloride), Toxaphene and Dieldrin, must be substituted.

Infestation with head lice, body lice or pubic lice can be quickly and easily controlled with 10% DDT powder. The powder is blown onto the body surfaces with an appropriate blower. The clothing, which should also be dusted, should not be changed for several days. The residual effect of the powder in the garments will serve to kill the newly hatched insects. Impregnation of underwear and other articles of clothing with DDT emulsion is effective in killing lice, even after 6 to 8 washings. Garments are impregnated with DDT by dipping in a 2 per cent emulsion and wringing moderately dry.

Fleas.—*Effective control for 3 months is obtained by premise dusting* with 5 per cent DDT in pyrophyllite or talc. DDT emulsions are also effective when carefully applied. DDT in oil sprayed lightly over breeding areas is effective. The insecticide should be dusted into the bedding of pets, the furniture, and rat runways and entrances.

Prophylactic Immunization.*—Protection against many infectious diseases can be developed by immunization. All persons should be immunized against smallpox, tetanus, typhoid and paratyphoid fevers, regardless of their place of residence, but especially in the Tropics where these diseases may be prevalent.

In the case of smallpox, a vaccine of proved potency administered by the *multiple puncture method* should be given at least every 4 years. The standard triple vaccine against typhoid and paratyphoid A and B is usually administered in 3 subcutaneous injections 1 week apart, 0.5 c.c. for the first dose and 1.0 c.c. in the second and third weeks.

To immunize against tetanus, alum precipitated tetanus toxoid is given intramuscularly in two 0.5 c.c. doses, 4 to 8 weeks apart. Duration of immunity

*See Chapter 1.

to tetanus is not as yet known, but it probably lasts several years Subsequent "booster" doses of 0 5 c c stimulate a rapid increase in protective antibodies *Booster doses are commonly given 1 year after the original immunization* and thereafter at 4 year intervals Emergency booster doses may be given when it is felt necessary, for example following contaminated lacerations or other types of injuries

Yellow fever vaccine should be given to all persons residing in or traveling through known endemic areas These areas are generally considered to lie in Africa and the adjacent islands between 20° N and 13° S latitudes and in South America between 13° N and 30° S latitudes On the South American continent the presence of yellow fever has been proved only in the northeast and central portions* Only vaccines of proved potency from a reliable source of supply should be used, because the virus deteriorates rapidly when exposed to higher temperatures Careless handling may render the vaccine completely inactive The concentrated vaccine is diluted 1 10 and 0 5 c c of this dilution is given subcutaneously The developing immunity persists for 4 years or longer

Immunization against typhus should be practiced during residence in endemic areas and during epidemics Two subcutaneous injections of 1 0 c c each at intervals of 7 to 10 days is believed to confer some immunity against murine and epidemic typhus for several months Experimental work on other rickettsial diseases, such as tsutsugamushi and spotted fever, may soon yield protective vaccines for these conditions

Cholera and plague vaccines are available and should be administered when the risk of infection is great as during epidemics, however, the immunity developed is of only questionable degree and duration

Although clinical diphtheria is relatively uncommon in tropical areas, cases do occur, and during the early years of World War II many cases of dermal infection were encountered in troops exposed to desert conditions in North Africa Therefore, under special circumstances, particularly when exposure to clinical diphtheria has been suspected, immunization should be practiced by the use of toxoid preparations It should be remembered, however, that even in tropical areas where diphtheria is uncommon, the majority of adults possess a relatively high titer of immune antibodies

Housing—Suitable housing is an important factor in the Tropics Proper location as well as certain types of construction can do much to minimize heat and dampness In general, houses should be built on high terrain so as to take advantage of maximum air movements and drainage Shade trees are desirable Two main types of dwellings for tropical areas have been developed first, those peculiar to desert climates, where there are large daily variations in temperature which have thick walls, little window area, and central patios, and second, dwellings in jungle climates, distinguished by large verandas and many windows The first type maintains a more nearly

*Since this chapter was written an outbreak has occurred in Panama

constant temperature inside and keeps out the undesirable hot winds T
second type gives maximum ventilation and shade

A variety of building materials from the primitive mud and thatch
hollow tiles may be used in tropical dwellings In general the builder shou
insulate to keep out the heat hollow tile or wood with hollow walls
suitable for tropical construction Peaked roofs are cooler than flat roo
because they provide more dead space and get less direct solar radiati
Galvanized iron which is very commonly used as roofing material in tropi
areas should be combined with an insulated dead space below otherwi
the effect is oven like during the hours when the sun is high

Roof gutters as a rule are to be avoided particularly in regions whe
mosquitoes are numerous Gutters frequently become clogged with leav
and debris pools of water are formed which provide breeding spaces for
sects The gutters must be inspected and cleaned regularly

Windows and doors should be screened to exclude mosquitoes flies a
insects It is true that screening eliminates a certain amount of air and mak
houses hotter but this minor disadvantage is greatly outweighed by the add
comfort and safety which screens provide Various types of metal screeni
may be used and there is a plastic screen which is said to be more dural
and lasting

Air Conditioning—Air conditioning which has had its widest use in tei
perate climates largely because of economic factors is becoming increasing
popular in tropical regions Many towns and cities in the Tropics have ai
conditioned buildings (theaters office buildings and cafes) Few priva
homes are air conditioned With increased production of low cost units mo
tropical residences will probably become air conditioned

Three factors determine conditions of optimum comfort temperatur
humidity and air motion There is a wide range of humidity roughly fro
30 to 70 per cent in which comfort may be obtained providing the facto
of temperature and air movement are properly adjusted Most people hov
ever feel uncomfortable if the humidity is less than 30 per cent or more tha
70 per cent The temperature range for comfort is approximately from 65
F to 85° F depending on the humidity (Allen and Walker 1939) The ten
perature of air conditioned rooms should be adjusted so that the differenc
between outside and inside temperatures is not too great During hot season
when air temperatures may be 90° F (32° C) or more the indoor temper
tures should be maintained near the upper limit of the comfort range

The benefits of air conditioning are unquestioned Prickly heat for ex
ample which can be annoying or frequently disabling in those whose skin
are constantly drenched in sweat disappears when environmental condition
are properly adjusted

LIFE IN THE BUSH

Traveling through unsettled regions in comfort and safety presents spe
cial problems anywhere but they are more numerous in tropical areas be
cause of the higher temperatures increased requirements for fluid and addec

disease hazards In many regions most foods clothing equipment and medical supplies cannot be procured locally and must be carried along from the starting point A few general remarks on expeditions in the Tropics are indicated

Food—The planned diet will vary somewhat with individual tastes and pocketbooks but certain staples are essential such as brown rice black beans sugar, coffee tea chocolate and bacon when available Dried and canned meats keep well and supply necessary proteins Dried milk in sealed tins will usually keep for many weeks or months and has a high food value Other dried foods such as soups and eggs have high caloric value in spite of the small weight and volume and offer agreeable additions to the menu Frequently, persons on long trips with a monotonous diet have a great craving for sweets which sweet chocolate or jams may satisfy When it is anticipated that fresh foods will not be available for many weeks it is advisable to carry a supply of vitamin preparations to prevent deficiencies

Sufficient drinking water for a 24 hour supply should be boiled each day allowed to cool and put in canteens or other containers

Clothing—Clothing should be above all cool comfortable durable and washable Short sleeved shirts and short trousers for daytime wear with long sleeved shirts and long trousers for use after dark should be made of lightweight khaki For head covering a straw hat or light pith helmet with waterproof covering should be provided Heavy boots of ankle length should be worn if the terrain is rough and much walking anticipated Otherwise low canvas shoes will be found to be more comfortable and serviceable Socks should be of lightweight wool or cotton and wool mixture Enough clothing should be allowed for frequent changing and washing A waterproof poncho or lightweight raincoat should be kept at hand for the sudden heavy rains which frequently occur and a good umbrella is often very useful

Sleeping Equipment—Collapsible canvas cots or hammocks are comfortable light in weight and take up little space They should be equipped with special mosquito nets with supporting frames for protection against insects Air mattresses for use with canvas cots are recommended by some travelers but others consider them a needless luxury An extra blanket folded double will serve very well as a mattress Blankets are essential for the nights frequently are cool

Bathing Facilities—To insure comfort and to promote skin hygiene facilities must be provided for bathing Collapsible rubber bathtubs which are light in weight together with a water bucket which may be made of canvas and an ordinary bath sponge will provide a convenient shower bath In this connection it is to be recommended that surface waters chiefly in areas where schistosomiasis is prevalent should always be suspected of being contaminated

Medical Supplies and Equipment—The quantity and variety of medical supplies will depend on the size of the expedition the anticipated length of time away from medical facilities and the kind of disease hazards to be en

countered However certain items are essential These include antimalarial drugs such as Atabrine in tablet form and in ampules for parenteral use and one of the newer synthetic compounds Aralen (chloroquine) 7 chloro-4 (4 diethylamino 1 methylbutylamino) quinoline (Board for Coordinatin of Malaria Studies 1946) The latter drug which is superior to Atabrine in many ways and is nontoxic in ordinary therapeutic doses has been released by the National Research Council and is available to the medical profession generally Other things which should be included are remedies against amebic and bacillary dysentery hypnotics and analgesics antiseptics skin ointments insect repellents and insecticides

A minimum of surgical supplies will be needed such as cotton sterile gauze squares bandages forceps scalpels suture needles suture materials syringes hypodermic needles and suitable sterilizers Appendix 1 page 1447 contains a list of suggested medical supplies and equipment which may be expanded or curtailed according to the needs of the party

The major part of this equipment should be packed in water tight tin trunks with a list of contents fastened to the insides of the lids Small supplementary first aid kits may also be carried to eliminate the necessity of opening the larger containers to remove small frequently used articles

COMMUNITY SANITATION

Sanitation of the environment on any large scale can be accomplished only by concerted community action The extent and efficacy of sanitary measures will depend largely on the education of the population in sanitary matters and the amount of money and trained personnel available The most rudimentary and necessary elements of sanitation are of course adequate and safe water supplies sewerage systems and facilities for disposal of refuse and garbage In many small towns where community water supplies are not feasible individual household supplies which are adequate and safe may be established Most surface and ground waters require some form of treatment to render them potable Various types of sand filtration settling and coagulation and treatment with chemicals particularly chlorine can be used according to the needs and resources of the community

Sewerage systems require in addition to the system of collecting pipes a safe method of disposal of the sewage Where community collecting and disposal systems are not feasible septic tanks may be a solution Other methods of sewage disposal may include the most suitable types of bored hole and pit latrines A system of sand buckets and collecting wagons with final disposal in septic pits has been found adequate in some communities

The disposal of refuse and garbage is an important disease control measure for accumulations favor breeding of flies and rats Fly tight household containers a regular collecting system and ultimate safe disposal are essential Refuse and garbage are commonly destroyed by incineration by burial or in some places by the compost method

Control of specific diseases is often possible only through community action. This is especially true when diseases are insect borne, such as malaria and typhus, or transmitted largely by water, food, and flies, as gastrointestinal infections. The control of malaria rests mainly on the destruction and elimination of the mosquito vector. Mosquito breeding places may be eliminated through draining or filling. Larvae may be controlled by the use of oil, Paris green, DDT, or other substances; the adult mosquito may be attacked with DDT or some of the pyrethrum preparations. The control of typhus depends on the elimination of rodents, fleas, and lice. The control of gastrointestinal infections is attained through purification of water supplies, reduction of flies, and the control of food handlers. Details of specific disease controls are presented in other chapters.

APPENDIX

Suggested List of Medical and Surgical Supplies

I Antimalarials
- 1 Atabrine in tablets of 0.1 Gm
- 2 Atabrine in ampules of 0.2 Gm (ampules of distilled water)
- 3 SN 7618 in tablets of 0.1 Gm and 0.3 Gm

II Antidysenteric
- A Amebic
  - 1 Emetine in ampules of 0.60 Gm
  - 2 Carbarsone in tablets of 0.25 Gm
  - 3 Chiniofon in tablets of 0.25 Gm
- B Bacillary
  - 1 Sulfadiazine in tablets of 0.5 Gm
  - 2 Sulfasuxidine in powdered form
  - 3 Sodium bicarbonate in 0.5 Gm tablets
- C General
  - 1 Camphorated tincture of opium
  - 2 Bismuth subcarbonate powder

III General Remedies
- 1 Morphine in syrettes (30 mg.)
- 2 Aspirin in tablets of 0.3 Gm
- 3 Codeine in tablets of 30 mg
- 4 Sulfanilamide in powder
- 5 Magnesium sulfate in bulk
- 6 Cascara sagrada in tablets of 0.3 Gm
- 7 Tetanus toxoid
- 8 Tetanus antiserum
- 9 Caffeine sodium benzoate in ampules
- 10 Antivenin

IV Preparations for External Application
- 1 Sulfur ointment (15 per cent)
- 2 Zinc oxide ointment (20 per cent)
- 3 Calamine lotion with phenol
- 4 Insect repellent (dimethylphthalate 6 parts, Rutgers 612 2 parts, Indalone 2 parts)

V Surgical Supplies

1 Syringes 2 c c, 5 c c, and 10 c c
2 Hypo needles in assorted gauges and lengths
3 Scalpel handle and blades
4 Hemostatic forceps
5 Thumb forceps, rat tooth
6 Thumb forceps, smooth
7 Dental forceps
8 Suture needles
9 Suture material, sterile
10 Cotton wool
11 Gauze bandages, 2 inch and 3 inch
12 Adhesive tape (tropical packing)
13 Elastic bandages
14 Wooden tongue blades
15 Ointment tins
16 Ethyl chloride ampules
17 Phenobarbital, or other intravenous anesthetic
18 Ether

VI *Miscellaneous*

1 Novocain crystals in ampules
2 Sterile distilled water in ampules
3 70 per cent alcohol
4 Mercuric chloride tablets
5 Yellow mercury oxide ointment
6 Dried blood plasma

VII Insecticides

1 DDT (dichlorodiphenyl trichloroethane) in powder, 10 per cent in talc or other vehicle, DDT, 5 per cent solution in oil
2 Spray gun for liquid and powder blower for powdered form

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CHAPTER 67

ORGANIZATION OF PREVENTIVE MEDICINE AND RURAL HYGIENE SERVICES IN SPARSELY SETTLED TROPICAL COUNTRIES

Gustavo Pittaluga

The general principles methods and technical procedures to be adopted in organizing services or centers of rural hygiene have been established for some time Using the practical example of the United States as a basis the First Conference on Rural Hygiene at which I had the honor of presiding was called by the League of Nations in Geneva in June 1931 Rules for undertaking projects similar to those undertaken by the United States were established with special consideration of the sanitary situation of rural communities of various countries of eastern Europe In some American countries however especially in tropical America there is a different problem that of *sparse settlement* which makes the organization and work of sanitary services difficult

There is a minimum of certain requisite conditions without which it is almost impossible to undertake public administration of rural commmunities scattered over a large territory especially in the Tropics which require special services to investigate and protect against pathogenic agents We must first establish limits within which intervention by the state or by public administration in sanitary regulations and in indicated geographic and demographic situations is possible Certain technical norms must be defined as to the hygienic sanitary situation of a country or sparsely settled district before undertaking installation of services or rural health centers

We shall summarize the types of diagnostic epidemiologic and sanitary services and their organization in countries and communities with the requisite conditions especially those in intertropical zones with hot climates where special human pathology is known or is presumed to exist

DENSITY OF SETTLEMENT AND ORGANIZATION OF RURAL HEALTH SERVICE

Preventive medicine in rural regions cannot be organized without previous geographic and demographic knowledge which exclusive of all epidemiologic or medical statistical data establishes the density of settlement in a determined zone or region (Revelli 1926) This knowledge has been acquired in almost all territories of various nationalities in the old European continent Neglect of this factor develops serious obstacles in some countries especially eastern Europe and thus the number of inhabitants who receive preventive medical assistance is not proportionate to the area over which such population is spread

Many settlements in different countries states, dominions, and colonies in Africa and Asia, and some in America, still depend upon indirect methods although work on this subject has progressed constantly since the middle of the nineteenth century, being especially notable in recent years

Density of settlement is known only approximately in such places as the Niger Basin, where *there are numerous heavily populated villages, and in the* high tablelands of central Africa or Tibet in central Asia, zones of extremely sparse population In some zones, particularly in western and equatorial Africa, penetration and protective work by sanitary services, especially the French and English, has also laid the basis for demographic knowledge of indigenous communities This almost titanic effort may serve well as an example for those projects which still present great difficulties in certain zones *of Central and South America*

For activities of a technical order, there are always required (1) direct action of a technician or functionary over a group of people assigned him, (2) means of communication and transportation sufficient to enable him to exercise this direct action within the radius of the territory, and (3) some cohesion of the scattered population, though it may be very elementary, and a certain solidarity, both material and moral, among community units *(families, farms, villages, etc)*

In some zones of the Western Hemisphere these conditions are far from being fulfilled

In northern Canada or in Alaska we still find small, scattered foci of hunters and fishermen, the population density being about 0 02 per square kilometer (barren ground), other geographic circumstances, orographic and hydrographic, determine similar conditions in the heart of tropical regions, namely, on the banks of great rivers in Brazil and Venezuela, on the high plateaus of the Andes of Bolivia, Peru, Ecuador, and Colombia

Bolivia, with an area of 1,834,000 square kilometers, has a population of 2 800,000, a theoretical density of 1 9 persons per square kilometer, but for purposes of studying rural life and the possibility of establishing medical aid or public sanitation service the real density is far from this figure If we eliminate the cities of more than 5 000 inhabitants which together include approximately 500,000 people, the rural average then would be approximately 1 2 inhabitants per square kilometer, however, the differences in certain regions are extremely marked For example, in the province of Potosi, we find in some districts (Frias) a density of 16 persons per square kilometer, in others a density of 0 09 In districts of a tropical region such as *El Beni (Trinidad) there is approximately 1 per* square kilometer, this is maximum In the districts of El Oriente and in the Gran Chaco in Brazil and Paraguay, density decreases to less than 0 5 per square kilometer

Even without considering means of communication, transportation and interchange *of food and other products over the vast area of the country we can still appreciate, from* the population density, degree of culture, and differences in race (whites, Negroes, half castes, and various immigrants), the immense difficulties which the public administration in Bolivia must overcome to undertake efficient steps to better rural conditions

In the famous volume of Bolivian photographs by Gerstamm (1928) (an indispensable document for anyone who intends to study social, demographic, and health problems and questions of that country), there prevails an impression of rural life far removed from the concept of the average rural environment of Europe or the United States that is, it is rather a primitive natural existence, scarcely touched by the influence of Spanish culture

In recent years, the situation in the field of public health has been somewhat modified by the valuable collaboration of the International Health Division of the Rockefeller Foundation In 1942, the Bolivian government created a special service to combat yellow fever, malaria, and ancylostomiasis through diagnosis and treatment of patients and through adequate education of the local sanitary personnel The problems inherent in a demographic situation so beset with difficulties have been observed at close range and solved in part by the technicians of the Rockefeller Foundation and by Bolivian health authorities in such places as banana, coffee, and other plantations in the province of La Paz and the valley of the Cochabamba In these places especially in the valley of the Cochabamba there was a severe outbreak of malaria in 1940 and 1942 an average of 15 per cent of the population was attacked, with some areas showing a much higher percentage The Anopheles mosquito develops in the running streams of Bolivia It was necessary to study its biology methodically so that special prophylactic measures could be instituted, adapted to an environment characterized by scattered population, lack of education, and general underprivilege

In 1935 719 cases of typhoid fever 16 cases of plague, 490 cases of smallpox, 1,244 cases of exanthematic typhus and 27 deaths due to yellow fever were reported in Bolivia The Ministry of Health knowing the demographic situation realized that these data represented only a part of the true situation

Since 1932, when a severe epidemic of yellow fever broke out in the lowlands of eastern Bolivia a special service in collaboration with the Rockefeller Foundation has studied foci of the Aedes mosquito the vector of the virus By 1943 this service announced negative results by viscerotomy in 45 rural centers Despite the difficulties due to lack of transportation this service had carried out a vast program of vaccination against yellow fever in three fourths of the area attacked by " jungle yellow fever "

Venezuela, some years ago undertook a vigorous public health program In the Health Education Center in El Valle in 1944 under the direction of Sahagun Torres, the Anti Venereal Service handled 610 patients and made 2 280 serologic tests (Kahn) The Prenatal Hygiene Service examined 790 patients (237 new patients) There were 414 births, during this period in the entire area under the jurisdiction of the Center, 237 patients were under the care of the Center during their entire period of gestation The Pre School Hygienic Service held 444 consultations There were 903 vaccinations administered against smallpox, 272 against diphtheria and 113 against typhus As a special project, we may mention an accelerated campaign against schistosomiasis, with 407 new cases coming to the Center during the year, and finally visiting nurses allocated to the Center made more than 4,000 visits (Sahagun Torres, 1944)

In Venezuela establishment of small rural centers of this kind throughout the extensive territory, the greater part of which is sparsely populated produced excellent results It should be added that the National School of Nursing located in Caracas and created in 1941 with the aid and collaboration of the Rockefeller Foundation (1944), contributed to the efficiency of these centers

Included in the large territory of Brazil are states such as Sao Paulo with a population density of 32 inhabitants per square kilometer (area 247,239 square kilometers, population 7,820,000) there are others in the interior of the country (Mato Grosso Pará, Amazonas) with a population density of not more than 4 inhabitants per square kilometer, and in certain regions of the equatorial jungle there is scarcely 1 inhabitant per 10 square kilometers A situation of this kind as seen in large areas creates serious social and health problems for the government The extraordinary difficulties of administering such a health program become apparent as soon as a government proposes, as Brazil has recently done, to undertake the task of improving hygienic conditions of the inhabitants The work necessarily must be limited to the study and solution of concrete problems requiring scientific investigation (jungle yellow fever or plague in rural surroundings, or leprosy, *because of the danger of spread) and carried out by experts, and also to supplying to this* sparse, widely scattered population modest medical and epidemiologic assistance, sometimes quasi medical offered by medical students and practical nurses

This twofold endeavor has been carried on in Brazil with satisfactory results (There is no reference here to the excellent sanitary institutions in the large urban centers of Brazil nor to the work of Public Welfare and Scientific Centers, which, in cities like Rio de Janeiro, São Paulo, and others, place Brazil among those model nations which are successfully solving problems of public health)

In discussing special epidemiologic problems, I shall report the work undertaken more than 20 years ago in the control of yellow fever—a project which, in 1932, led to the important discovery by Soper and his collaborators that yellow fever exists independently of the transmitting mosquito, *Aedes aegypti*, in the rural communities of Brazil During the years of investigation (Soper et al, 1933, 1934, 1937, 1938, Annual Report of the Rockefeller Foundation, 1935, 1944), the International Health Division of the Rockefeller Foundation expended, up to 1943, more than four and one half million dollars, in close collaboration with the government of Brazil

Although all the reservoirs of virus of yellow fever are not yet known—those sylvatic animals which harbor the virus during the long periods of latency between epidemic outbreaks which still occur among isolated workmen—scientific and prophylactic contributions have been remarkably successful, thanks to the special Viscerotomy Service, making more than 25,000 examinations of liver tissue in other individuals and ultimately (1944) to the creation of a field laboratory in the southern part of the state of Bahia in Pontal

As the result of the examination of hundreds of sylvatic animals, monkeys, opossums, and various other marsupials a yellow fever virus animal carrier, which had died with this disease, was found in June, 1944 This was the first time that this had ever been observed in nature The mosquito fauna of the forest regions of Brazil have been studied thoroughly, entomologists collaborating with the Yellow Fever Service have described new species of Aedes and also related species (Davis, 1944, Waddell, 1945, Cerqueira and Lane, 1944)

Another problem of more than ordinary importance in Brazil is that of leprosy To gain an impression of the difficulties until recently encountered in gathering demographic data concerning leprosy in scattered population groups in most American countries, consult the statements of McCoy in McKinley, *Geography of Disease* (1935) Figures given of the number of leprosy cases in some countries are only one tenth of the actual number of cases, judging by later investigations which not even today can be considered as complete The figure given for Brazil in 1935 was 6,655 cases Since the establishment and development of the International Center for the Study of Leprosy in Rio de Janeiro, and since the contributions of the leprologists of São Paulo* have been published, the figures stand at 35,000 as the *minimum* number of cases of leprosy in Brazil The uncovering of some 15 of these cases in the tiny nucleus of settlements in the forest regions represented the difficult work of years This work could not have been accomplished without the aid of technician specialists General public health and welfare agencies cannot assume this function, except as auxiliaries to specialized leprosy services

In the region of the upper Amazon and in the forest belts of central Brazil, there exists, properly speaking, not a true rural community, but rather a natural, unorganized existence To locate the widely scattered natives for the purpose of studying their customs, primitive agricultural activities and food habits it is necessary to undertake a veritable exploration Such trips as those made by T Koch Grunberg Hamilton Rice, Holdridge Schwez, Hanson and others merit recognition inasmuch as they are concerned with demographic sanitary questions (National Geographic Magazine, 1929 1935) Hygienists and administrators interested in the situation from the social and economic point of view should consult Maurette (1937) in a publication of the International Labor Bureau "Among countries of the interior as well as coastal countries, Brazil has the greatest extent of unsettled fertile territory in Latin America The vast extent of this

*The International Center for the Study of Leprosy of Rio de Janiero was set up under the auspices of the League of Nations in 1932 and later placed under the direction of Professor Rabello of the University of Rio de Janeiro

exploitable land has enabled Brazil to absorb millions of immigrants during the past fifty years. The country is still capable of receiving many more millions necessary for the development of the country.

These economic demographic problems will eventually produce great health problems. To avoid risk of unexpected epidemic outbreaks in new immigrant groups special care is required in organizing health services and in placement of personnel. This activity should demand of newly organized companies and of industrial and commercial centers a direct economic participation in the health program under the administration of the Department of Health of the state.

Governmental authority now has at its disposal excellent demographic and cartographic data which permit establishment of a scale of possible activities in the field of health and hygiene.*

The study published by Shattuck and his collaborators (1933) offers an example of thorough documentation; without it the results obtained by public health services might not seem to justify the effort put forth in the undertaking (Martinez 1943). In my judgment, previous monographic studies are indispensable in establishing a basis for public health service on no matter how small a scale in a sample district, especially in tropical countries with sparse population. These studies may be of two types: (1) a study of one specific problem, in which case the study may extend over a larger territory, or (2) a study of the entire group of sanitary problems, in which case the study would be carried out over a much more limited area (Shattuck et al. 1933; Alexander and Meleney 1935.)

In Mexico the problem of amebiasis is of primary importance in connection with etiologic diagnosis, treatment and prevention of dysentery in general. The situation in Mexico, although serious, has improved in recent years.

The problem is serious in all countries of Central America and in some countries of South America. In the great majority of cases even now the mortality statistics on dysentery do not differentiate between amebic and bacillary etiology (Birand 1933).

Some time ago physicians of the United Fruit Company in their work in rural communities of Colombia and other countries of South America found that up to 53.7 per cent and in some other places 40.9 per cent of the population were carriers of *Endamoeba histolytica*, many of these being ambulatory patients who were able to attend to their regular agricultural duties although in a poor state of health. Probably a large part of the fatal cases of dysentery registered in Mexico (1933-1936) were in reality cases of bacillary dysentery (Shiga and Flexner) or of dysentiform enteritis of a different etiology. This problem clearly requires an *unhurried differential diagnosis based on parasitologic and bacteriologic examination of feces*; further, it is clear that this procedure cannot be practiced unless numerous small laboratories can be installed in the rural sections connected with regional rural health centers. See Chapter 71.

All this requires time and special preparation of technical personnel. The desired results, epidemiologic and prophylactic, will be accomplished with less difficulty and more rapidity if certain conditions are fulfilled: (1) re

*American cartography has many means of establishing geographic and demographic ... in "A Cata ... Society, New ... published in ... Agriculture ... is very rare ... alesce[illegible] are ... [illegible] ers.

linquish the attempt to establish in every district and section true health and hygiene centers *which are expected to deal with all* epidemiologic and prophylactic problems, (2) limit, for the same reason the activity of the small rural laboratories to the study and solution of one or two of the most urgent problems in each division, (3) make these laboratories (with limited technical personnel and aids) mobile units with adequate means of transportation (*automobile laboratories*), for the purpose of overcoming the problem of reaching people scattered on farms in huts, and in rural dwellings of all types who are almost always widely separated from each other

This proposition is connected with the problem of rural housing Difficulties in solving this problem are enormous, yet it must be recognized that *domestic foci* of transmission of infectious and contagious diseases are essentially epidemiologic factors in countries with scattered populations Studies of this problem were initiated in Mexico particularly by Mazzotti (1933), and the administration recently began a campaign of public education and practical application of some exemplary measures to point the way to beneficial modifications of local customs regarding construction and arrangement of dwellings in rural surroundings Results of these efforts will not be apparent for a long time

Thus, we have attempted to draw certain conclusions for the solution of the most pressing problems of welfare hygiene, and public health in tropical countries with low population density

Orographic factors such as high mountains, plateaus, hills and valleys, as well as hydrographic factors, like rivers estuaries, etc exert a great in*fluence upon the population density because they modify climatic and social* conditions, ease or difficulty of natural communication, etc Acclimatization of the human being to living in altitudes above 3,000 meters such as the Andean regions, particularly in Peru, has given rise to new problems of health and hygiene peculiar to these conditions Monge (1928) and others indicated the effect of the processes of adaptation and their demographic results upon a people which has lived for centuries between 3,000 and 5,000 meters above sea level, with a special *pathology* and *sui generis* reactions against various pathogenic agents (Monge 1935)

These considerations might be extended, in relation to population density, its factors, and consequences, *to American countries with a temperate or cold climate* This is true of Argentina The average density of population in Argentina, exclusive of the capital cities, is less than 4 inhabitants per square kilometer The state of Jujuy has a population density of approximately 1 5 inhabitants per square kilometer, the territory of Rio Negro comparable *in size to* England, has 50,000 to 60 000 inhabitants, and Tierra del Fuego, at the extreme southern tip of Argentina, with an area as great as that of Belgium, has only 3,000 inhabitants Similar problems concerning density of population also exist in some of the states of the United States Before the war (1940), the state of Nevada, with the smallest relative population in the United States, had a population density of 0 3 persons per square kilometer, or 1 person per 3 square kilometers

In order to apply health measures or to organize a public health service a territorial study of the density of population must be conducted A study

of abstract figures dealing with a large expanse of territory will not suffice, since it accomplishes no more than a sort of preliminary theoretical orientation It is necessary to know how the population is distributed over concrete areas with determined physical characteristics This is not always easy to determine Topographic and sociologic delimitations of the territory offer difficulties In the words of Abbott Payson (1930), "One of the serious hazards in the study of early materials on population is the question of the extent of the area enumerated" It is necessary, within the limits of the area chosen for study, to estimate the topographic divisions condition of rural housing, distance, location in relation to highways, roads, rivers, forests, sources of occupation, natural wealth, and markets After this, epidemiologic work begins followed by selection of the type of welfare and health service, and the activities concerned in its installation

METHODS OF ESTABLISHING THE PREVIOUS SANITARY STATUS OF A GIVEN AREA

Once the population density in a given area has been established, it is necessary to ascertain in general terms the previous sanitary status before deciding upon the most appropriate procedure for application of health measures by mobile equipment small laboratories for investigation and prophylaxis, or true rural health centers

Three methods may be used, simultaneously, if the necessary elements are so arranged (1) The *empirical method,* which consists in gathering summary information in the selected area, from the natives themselves, from persons of authority among them, from physicians when there are any, or from local practitioners The data concern general mortality, infant mortality, the most common and most serious diseases potable water basic diet average type of housing, presence or absence of latrines or special places for defecation and collection of excreta, and the presence of domestic animals, as well as their distance from the houses (2) The *epidemiologic method,* involving a period of 3 to 6 months consists in a scientific research by a technician, a medical specialist in epidemiologic work, for data on local predominant pathology making use, of course of observations obtained by method 1, and paying special attention to local fauna particularly to those insects which may be possible vectors or transmitters of disease (3) The *statistical method,* which consists in the examination and study of data (when they exist or when it is possible to gather them) concerning mortality, disease, and birth, with all the accessory elements for a period of several years The work may be carried out by an expert in demographic statistics, but in urgent cases or in a situation requiring less responsibility the work may be entrusted to employees of the administration of a nearby urban center

In 1936 Stouman and Falk published an excellent study on health indices of determined communities Even before this a group of United States hygienists under the direction of Professor Winslow of Yale University, had worked out (1920 1935) a series of indices and norms for the evaluation of

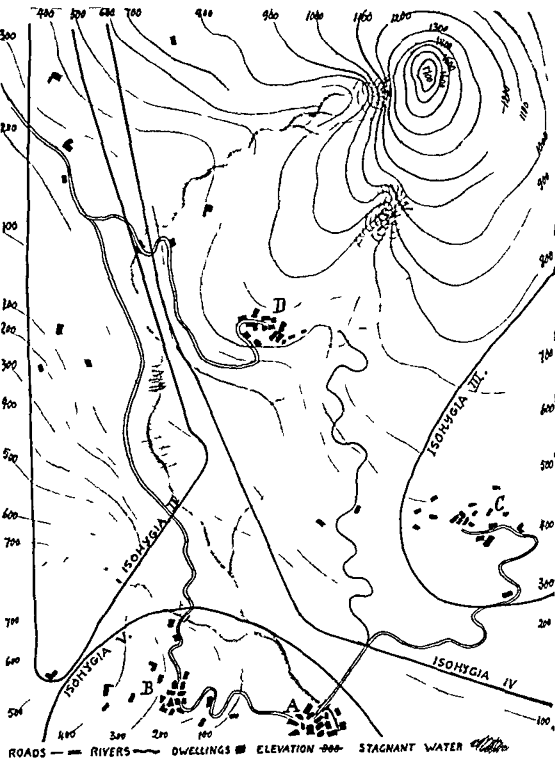


Fig. 459.—(Legend on opposite page.)

the practical efficiency of the work in public health The research to in certain districts and sections of the United States However the adopted by these investigators are not entirely applicable to a proj preliminary examination since the latter deals with a situation as before the intervention of health activity and in the absence of any org of public health in low density rural populations in tropical countri study by Stouman and Falk also refers in general to health indice itary indices of communities principally in the United States Stour published a monograph on health indices of the city of New Haven These proposed indices were later discussed and accepted for Europe tries by the Section on Hygiene of the former League of Nations (1938) Some of these indices proposed by Stouman and Falk may advantageously in a study of previous sanitary situation of rural com which have as yet not been hygienized

The Stouman and Falk indices include three groups of data (and health indices (2) environmental indices and (3) indices of adm tive health activity

The second group of data those concerning environment incl climate (b) density and topographic distribution of the population termined area (c) social and professional division of the population tural level (e) division of property and economic situation (f) ille births and prostitution (g) housing (h) diet and (i) consumption holic beverages

During the period 1937 1938 I studied this problem having been with the preparation of a report for the Second International Confe Rural Hygiene which was to have been held in Mexico in 1939 but wl cancelled due to the war I intended at that time to express the ir

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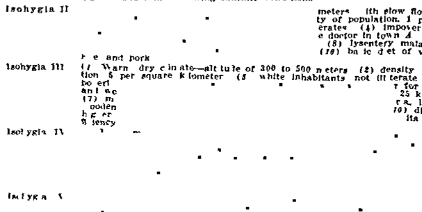


Fig 459—The isohyg as n this map ind cate that the population included w limit of the i ohyg a is under the fol owing sanitary cond tions

Isohygia II meters ith slow flo ty of population. 1 p erates (4) impover e doctor in town A (8) dysentery mala (10) ba ic d et of v F e and pork

Isohygia III (1 Warm dry c im ate—alt tu le of 300 to 500 m eters (2) density tion 5 per square k lometer (3 white inhabitants not ill iterate bo eri an l wo (7) m ooden h g er 8 iency r for 25 k r a l 10) di ita

Isohygia IV

Isohygia V

sanitary status of determined areas by means of a cartographic proce by means of curves indicating the sanitary situation and its limits so the final differences between the status of one location and that of ano could be indicated simply although always in approximate and variable f I suggested the term isohygias' for these cartographic curves (Pittal 1939) to be used somewhat as the term isotherms isobars and isochrones used

These terms are all conventional and relative to a unit of measure es lished conventionally by man

The most typical example because of its similarity to the term isohyg is the term isochrone' proposed years ago by Bartholomew (1906) chrones are cartographic lines showing equal distances between diffe points in a territory based upon a vehicle of known and constant velo They are useful for commercial purposes The concept is of course t retical since vehicles vary greatly in velocity in a given unit of time much the same way although with slower rate of variation the health si tion in a given locality may be indicated While the factors in the situa are variable this does not prevent establishment of the actual status quo consideration of great importance in using isohygias (to give a fairly c plete picture) is to fix accurately the element and the degree in the situat The necessary and sufficient elements in our opinion are (1) climatic physical characteristics of the territory (2) density of population ethnographic characteristics and cultural level (4) total economic capa and division of wealth (5) types of occupations and working conditio (6) the present level of technical health program by the state or local ministration (7) available demographic figures (mortality morbidity b rate etc) (8) epidemiology especially local (9) characteristics of the lo rural housing of the indigenous population and (10) characteristics of diet of rural indigenous people

These data may be gathered by one of three methods given above or using them together or successively

The type and grade of each of these 10 elementary conditions may designated by Roman numerals (I II III IV etc) so that by combinati there are established 10 different isohygias as represented in Fig 459

With this method a graphic presentation which can be easily noted be made of sparsely populated regions or regions with sparsely popula zones with special physical characteristics Such graphic presentation is use as a basis in organizing a health service which will be adequate for specific lo requirements and the foreseeable hygienic situations

TYPES OF DIAGNOSTIC EPIDEMIOLOGIC AND HEALTH SERVIC APPLICABLE TO REGIONS OF LOW POPULATION DENSITIES IN TROPICAL CLIMATES

The *Memorial published in Geneva as a result of the First Internatio* Conference on Rural Hygiene in 1931 * following the successful attempts ma

in the United States established the 'guiding principles of organization of medical assistance health and sanitation services for rural districts with an attempt to define the limits both in *area* and in the *number of inhabitants*, of the rural district accessible to such services'

It was not possible to find a criterion which would be applicable to all cases even when dealing with European countries The *Memorial* cites 50 000 inhabitants as the average number for each health district In reference to area and also to density of this population it is recalled that in Denmark such districts are between 700 and 800 square kilometers while in Yugoslavia there are districts which extend over 10 000 square kilometers or more

The principles adopted in the *Memorial* imply an organization of true health centers with definitely technical service preventive medicine protection of mothers and children antituberculosis program etc In situations such as we find in the various countries of South America, where planning must be done for many different regions creation of such complete services cannot be considered In such regions they must be reserved for the urban centers for which they may serve as coordinators and to some extent as the directors of activities of rural services

Leaving local differences to decisions of health authorities three types of health service may be suggested differing from each other in size and importance in personnel and equipment and also in function

1 The first type which will be referred to as elementary is to be thought of as a simple dispensary under the direction of a physician who has attended for at least one year a special course in a school of tropical medicine and public health and who aided by two nurses and a small personnel recruited in the district discharges the following duties (a) parasitologic examination of feces (b) microscopic examination of blood (c) serologic tests, (d) general medical aid in urgent cases with distribution of therapeutic and prophylactic medicaments (e) empirical and eventually statistical inquiry into mortality and local morbidity and (f) direct education of the local population concerning problems of hygiene through small conferences the use of radio and motion pictures and other means

The equipment necessary for a small elementary dispensary of this type is minimum The dispensary may be housed in two rooms of a residence which may be rented or otherwise provided It must possess means of transportation adequate to the topography distances and points of communication existing in the community An automobile is indispensable with eventually additional means of transportation

With the means of research (enumerated in *a* *b* and *c*) available the physician in charge of an elementary dispensary of this type is able to diagnose helminthic diseases or intestinal parasitic metazoa amebic dysentery or other intestinal protozoan diseases malaria microfilaria in the blood of local patients hemopathy in general syphilis eventually yaws and infections diagnosable by serum agglutination tests (typhoid and paratyphoid fevers etc)

Through the initiative displayed by the physician if time permits subsidiary investigation (not obligatory) and superficial inquiry may uncover

other local diseases Collections of insects and ectoparasites may be made to be sent for study to the larger centers with which the dispensary is associated

A very important function of the elementary dispensary because of the influence exercised over the local population by such services as distribution of medicines is to educate the local population directly through all available media especially by means of personal suasion and teaching on the part of the physician in charge of the dispensary

If there is a school teacher in the district and if the illiterate portion of the population is not too great posters leaflets and other illustrative material may be used with brief explanation of the transmission of parasitic diseases and infections Talks by the physician radio programs motion pictures—transportable media by which the entire territory of the district can be successfully covered—will serve better to achieve the concrete purpose of raising the cultural level of the population with significant improvement in the health status

The physician in charge of the dispensary should send a quarterly report to the health center of the district to which he belongs giving a detailed account of his medical service of the medicaments distributed and of analyses made within the period

2 The second type of service has a different objective In our opinion it should take the form of an epidemiologic laboratory Under certain conditions *this laboratory may be located in the same district or locality or even* housed in the same building as the elementary dispenary but its activities are to be independent The epidemiologic laboratory is to make a complete study by scientific methods demanding special equipment of one or more of the endemic or endemic epidemic diseases of the region

The laboratory is to be under the direction of an epidemiologist aided by one or more assistant experts in microbiology The radius of activity need not be limited to the area of the district the laboratory should have sufficient means to transport part of its personnel to various localities within its radius of operation It is not to be administrative it solely studies diseases It is not possible nor advisable to charge it with the general work of health education It is assumed however that the personnel *will also be required to adopt* health measures and will not refuse to instruct the local population or to give advice on needed health projects to control the endemic focus etc

The following diseases found in tropical countries with low population densities require establishment of epidemiologic laboratories dysentery yellow fever filariasis leishmaniasis malaria because of special characteristics of the biology of the mosquito vectors in some regions plague exanthematic typhus and rickettsioses in general

3 Cosmopolitan diseases the great problems of infantile mortality prenatal and maternity care housing diet the campaign against tuberculosis etc should be included in a third group of establishments designated public assistance and health centers '

This third group will serve as centers for coordination of the services of the elementary dispensaries and epidemiologic laboratories and will also fulfill other functions These large centers are to be directly under the administration of the state

The public assistance and health center of a given district or territory must be centrally located with respect to the boundaries of the territory with adequate means of communication so that it may with relative ease keep in touch with the two lower types of institutions under its jurisdiction

The public assistance and health center should be under the direction of a qualified hygienist assisted by an expert in health and demography by a physician who is a specialist in tuberculosis by a pediatrician and by a sanitary engineer The center should have a corps of nurses and visiting nurses Its essential functions are (a) coordination of data transmitted to the center quarterly by the elementary dispensary and eventually by the epidemiologic laboratory (b) prenatal and maternity care with a program of education for pregnant women and mothers (c) radiologic and biologic diagnosis of tuberculosis especially pulmonary tuberculosis and surveys of tubercular subjects and aid in domestic prophylaxis (d) parasitologic examination of fecal material blood examinations and serologic and biological testing of local patients (e) inquiry into home sanitary conditions and establishment of regulations of latrines and removal of excrement by the sanitary engineer (f) inquiry into vitamin deficiency and local diet with an educational program especially concerning diet in infancy and childhood and (g) courses in hygiene and health for local physicians nurses or special population groups

In the field of health education the functions of the welfare and health center differ substantially from those of the elementary dispensary in the methods used The dispensary is to be charged with education of the public by popularizing the subject of health and hygiene through general education The center is to offer a higher level of education through courses to physicians nurses and other specialists for the most part less typically rural groups since it may be supposed that the center will be located in a villa or some small urban grouping or in a town of the province

The public welfare and health center should be in charge of establishing and modifying the isohygia curves of the district or territory under its jurisdiction

The center should report every six months or once a year according to disposition made by higher health authority to the National Health Administration It should give an account of the progress of its work and of the results obtained with appropriate statistical summary and graphic representation of the variations covering a given period

CONCLUSION

Needless to say a nation to initiate and carry out a health program such as this needs (1) an economic basis of operation with annual revenue to be devoted exclusively to this work and (2) competent technical personnel especially trained in the field of sanitation epidemiology and public health

In the matter of public health, it seems to us that the state should not only not refuse private funds, but should on the contrary encourage all contributions from whatever organization or private initiative Experience shows that a health program such as this produces results only after many years of effort and long periods of uninterrupted work (Castillo, 1945)

A factor just as decisive as the economic factor is that of competent technical personnel Countries which face this problem should dedicate themselves to training specialized technical personnel with guarantees of employment in this work, proper remuneration, and sufficient authority, through long term contracts or appointments in public administration

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CHAPTER 68

OUTLINE OF HEMATOLOGY AS RELATED TO TROPICAL DISEASES

R B H Gradwohl

Hematologic laboratory diagnosis is very important in the study of tropical diseases The fundamental features are presented here as briefly as possible For fuller details see Gradwohl (1948)

The changes which occur in the blood as a result of physiologic adaptation by the resident of the Occident when he finds himself in the Tropics have been considerably discussed and no great changes have been authenticated Plasma volume has been studied by various authorities notably Talbott Edwards Dill and Drastich (1933) They reported that the small differences observed were within the limits of error of the method Drinker (1936) found that blood volume increased as the Tropics were entered Drinker stated that the necessary increase of sweating must require a constantly higher blood supply to the skin and if the blood volume did not increase impoverishment of the internal organs would result Forbes Dill and Hall (1940) found that white individuals who had moved to a hot damp climate had a small increase of about 5 per cent in the blood volume and in the plasma volume Many different writers have asserted that red cells may be increased and white cells decreased by residence in the Tropics Sundstroem (1926) in reporting on his observations on the blood of white residents of northern Australia found reduced levels for total phosphorus in the blood These findings have been at variance with those of other observers It may be generally stated that there are no definite changes in the blood actually due to residence in the Tropics

Preparation of Glassware for Making Blood Films

The cover glasses recommended are 7/8 inches wide, size ' B square

All new slides and cover glasses must be cleaned thoroughly before use to render them fat free Make up a weak solution of a detergent* by using about half a teaspoonful of detergent to a pint of warm water Admit the slides and cover glasses into this solution one at a time so that the entire surface of each is in contact with the wetting agent Allow them to remain in the solution for a period of 15 minutes to a few hours Do not leave them in too long because they might become coated and then cannot be used

Wash very thoroughly preferably in running water until all traces of the detergent have been removed Place them in warm water and dry immediately using a soft cloth Linen which has been washed many times makes an excellent towel for drying slides Use enough pressure in drying the slides to remove any traces of fat which may remain on the slides Have clean slides and cover glasses on hand at all times in the laboratory

If the slides have been examined under immersion oil and are to be kept dip them in xylol to remove the oil then holding them at an angle blot the xylol to the bottom of the slides These slides can then be stored or filed for future use

*We recommend Haemo Sol manufactured by Meinecke & Company 225 Varick St New York 14 N Y

If used slides are to be washed and reused remove the oil with a cloth containing a few drops of xylol and then clean in the detergent as directed above

With this method no boiling washing with soap or using equal parts of ether and alcohol is necessary Slides are clean and fat free without further processing Do not, however, allow the detergent to dry on the slides

Blood Stains

Giemsa Stain —

Considerable difficulty has been encountered by many workers in the manufacture of a serviceable Giemsa stain These difficulties have been overcome by following the formula of Lillie (1943) which is our recommended method

Azur B Eosinate

Dissolve 1.0 Gm methylene blue 85 88 per cent dye content
in 600 c c distilled water in a mortar
Add 0.8 c c of concentrated sulfuric acid sp gr 1 835 to 1 84
Bring to a boil
Add 2.5 Gm of potassium dichromate dissolved in 25 c c distilled water
Boil 20 minutes
Cool to 10° C or lower Place in the refrigerator overnight
Add 1.75 Gm sodium bicarbonate slowly with frequent shaking
Add a 5% solution of eosin Y of about 90% dye content and shake constantly until the margin of the fluid appears pale blue or bluish pink About 205 c c will be required Three fourths of this amount can be added at once
Filter at once preferably on vacuum funnel with hard paper
When fluid has been drawn through and the surface begins to crack add 100 c c of distilled water let drain and wash again with a second 100 c c of distilled water
Open out the filter paper and let it lie on a larger piece of filter paper or a paper towel and dry overnight on a warm plate or in the incubator at 37° C The drying may be accelerated by using two 100 c c portions of acetone or preferably 95% alcohol as washes after the second wash with water Drying at 55° C to 60° C has been tried and produces quite a little alteration of the thiazin dye less if acetone or alcohol washes are used and the heating limited to 2 or 3 hours The resultant dye is the *crude azur B eosinate*

Azur A Eosinate

Proceed as above for the azur B eosinate using 5 Gm of potassium dichromate instead of 2.5 Gm and dissolve it in 50 c c distilled water

Methylene Blue Eosinate

Dissolve 1.0 Gm methylene blue in 600 c c of cold distilled water
Precipitate as before with 5% eosin filtering and drying as above

Methylene Blue

Use certified methylene blue chloride

Solvent

Equal parts of glycerin and methyl alcohol (certified)

Lillie Stain

Grind the azur B eosinate azur A eosinate methylene blue eosinate and methylene blue (when necessary) separately into fine powder using separate clean mortars
Weigh 840 mg azur B eosinate
140 mg azur A eosinate
420 mg methylene blue eosinate
and 280 mg finely ground methylene blue

PLATE V.—BLOOD CELLS—GIEMSA STAIN

(1) Myeloblast
(2) Promyelocyte
(3) Neutrophilic myelocyte (form usually seen in myelogenous leucemia)
(4) *Neutrophilic myelocyte (form usually seen in infections)*
(5) Eosinophilic myelocyte
(6) Basophilic myelocyte
(7) Juvenile or metamyelocyte (neutrophilic)
(8) "Stab" (band form) (neutrophilic)
(9) Twisted "stab" (neutrophilic)
(10) Degenerated "stab" (neutrophilic)
(11) Segmented neutrophile
(12) Segmented eosinophile
(13) Segmented basophile
(14) Lymphoblast
(15) Large lymphocyte
(16) Small lymphocyte
(17) Reticuloendothelial cell
(18) Monocyte (formerly called "transitional")
(19) Monocyte
(20) Monocyte
(21) Endothelial element
(22) Atypical promyelocyte
(23) Micromyeloblast
(24) "Twin nuclear" cell of Schilling, seen only in leucemia (according to Schilling)
(25) Plasma cell
(26) Small plasma cell
(27) Polychromatic megaloblast
(28) Orthochromatic macroblast.
(29) Orthochromatic normoblast
(30) Orthochromatic microblast
(31) Normoblast with nucleus showing karyorrhexis
(32) Hyperchromic megalocyte
(33) Macrocyte
(34) Normocyte
(35) Microcyte
(32) to (35) Examples of anisocytosis
(36) Erythroblast with mitotic nucleus
(37) Faintly polychromatic erythrocyte
(38) Polychromatic erythrocyte
(39) Basophilic punctation, fine
(40) Basophilic punctation, coarse
(41) Poikilocytes
(42) Marginal granule
(43) Ring form of malarial parasite
(44) and (45) Cabot rings
(46) Hypochromic erythrocyte
(47) Hyperchromic erythrocyte
(48) Blood platelets

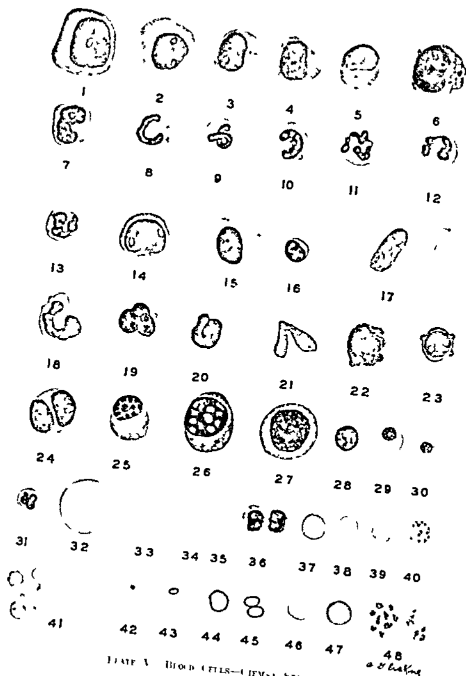


PLATE V. BLOOD CELLS—GIEMSA STAIN

(See explanation of figures on opposite page.)

Mix the 4 powders thoroughly, and pour over the surface of 200 c c of the solvent, in a brown bottle or flask Cork the container

Allow the powder to settle into the solvent gradually

Shake frequently for 2 or 3 days keeping the bottle between 50° and 60° C between shakings

If the bottle is tightly stoppered (the fluid level is marked on the outside with a wax pencil or a piece of adhesive), there will be little or no loss from evaporation and if there is the fluid level can be restored by addition of methyl alcohol

The glycerin should be neutral anhydrous and of the purest grade obtainable Use methyl alcohol special for blood work

Filter the stain through No 5 Whatman filter paper into clean dry dark bottles The stain is ready to use and is stable Use as for Giemsa stain original formula

Wright Stain.—

Wright Dye

0 5% aqueous solution of sodium bicarbonate	1000 c c
Methylene blue	10 Gm

Grind in a mortar until all the methylene blue is in solution Place in Erlenmeyer flasks to a depth of not more than 6 cm, and stopper lightly with cotton

Heat in an Arnold steam sterilizer at 100° C for one hour

Cool Filter through filter paper

To every 100 c c of the filtrate, add 500 c c of 0 1% aqueous eosin Y solution Add the eosin solution slowly, and stirring constantly to form a precipitate Test the solution for a free eosin ring by placing a drop on a piece of white filter paper and drying The ring appears as a faint pink halo around a lavender spot If the ring does not appear add more 0 1% aqueous eosin until the ring forms Our experience has been that between 700 and 750 c c of 0 1% aqueous eosin Y are required to exactly precipitate 100 c c of the polychromed methylene blue

Filter through No 5 Whatman filter paper, folded into four parts Discard the filtrate and save the precipitate on the filter paper Place the paper in an incubator to dry for several days This is the stock stain Place it in a dark bottle and store as "Wright Dye" The dye is stable

Wright Stain (Working Solution)

Dissolve 0 1 Gm Wright dye (above) in 60 c c of methyl alcohol acetone free Grind the dye in a mortar, adding the alcohol slowly until all the dye is in solution

Place in a dark bottle Allow to stand about 2 weeks before using

Filter through filter paper The solution is not always stable

Preparation and Staining of Blood Films

Discard the first 1 or 2 drops after the puncture

Pick up the slide with the left hand, holding it between the thumb and pointer finger Pick up a small drop of blood near the end of the slide, but do not touch the skin

Hold the cover glass between the thumb and the first finger of the right hand Approach the drop with the cover glass at an angle of 45 degrees When the cover glass touches the drop of blood, wait until the drop of blood runs across the edge of the cover glass, then gently pull it across the slide to form a thin film Do not put any tension on the slide or the cover glass. Draw the cover glass steadily, not fast not too slowly, pulling the drop of blood The cover glass is always in front of the blood The film should not touch the edges of the slides—it should be "margin free"

Allow the slide to dry in the air, then scratch the patient's name or identifying number in the thicker beginning end of the film (small writing)

If the film is not "margin free," the large cells tend to go to the edges and the small cells to the center By combining the margin free film with the "four field

meander" method of counting, differences in distribution of the cells due to the personal element should be almost entirely eliminated

Do not use too large a drop of blood, for the film will be too thick; too small a drop makes a very thin film, which is also objectionable To make thick smears, pull the cover glass faster, and to make thinner films, pull the cover glass more slowly

Staining Blood Films

(1) **Giemsa Stain**—The stock Giemsa stain keeps indefinitely, but the diluted stain must be made just before use, since it loses its staining qualities within an hour or more The container in which the stain is diluted must be free of acids and alkalies

It is well always to dilute the stain in the same container, and after using, to rinse the container thoroughly in warm tap water, then in neutral distilled water, but do not remove the small amount of dye which adheres to the glass The stain is better if made in a cylinder or flask with a thin coating of the stain From time to time wash out any precipitate that forms with hot tap water

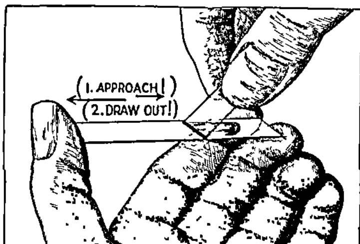


Fig 460—Correct method of making a blood film (From Schilling The Blood Picture, St Louis The C V Mosby Co)

Neutralizing Water for Staining Blood Films and Thick Drop Preparations Neutral distilled water is used in routine staining There are many methods of obtaining neutral water, but the method of choice is that using hematoxylin as an indicator and 1 per cent potassium carbonate as the neutralizing agent for acid water and 1 per cent hydrochloric acid for alkaline water In our hands, water neutral to hematoxylin has proved better suited to staining blood cells than has water with a pH of 6 4 We have found that water which is neutral with the use of hematoxylin as an indicator has a pH of 6 8 to 7 0 There are numerous buffer capsules that may be used, and these are better than not neutralizing the water at all, but our experience has been that cells stained with buffered water show very little of the important nuclear structures, and for that reason we do not recommend the buffer capsules except for emergency work

Method Neutralize enough water for the day's work The bottle used for storing the neutral water should preferably be Pyrex, or one should use a bottle which has held nothing but water for several months Silicates from the glass interfere with maintaining the neutrality of the water Do not use a rubber siphon, but pour the water from the stock bottle to the flask or other container being used for the day's work

Pick up a few crystals of hematoxylin crystals with a pair of forceps and place in a test tube which has been rinsed with the water to be tested Add about 5 c c of the water

and shake If the water is neutral it becomes a pale lavender pink or salmon color within 10 seconds If it is acid it becomes yellow and remains so for more than 5 minutes If it is alkaline it turns red and purple before 1 minute

If the water is acid use 1% potassium carbonate to neutralize it and if alkaline use 1% hydrochloric acid Add the neutralizing agent to the bottle of water a few drops at a time and shake thoroughly to mix Then test again and continue in this manner until the water is neutral as shown by a faint pink color within 10 seconds (without a trace of yellow or blue)

Water neutralized in this manner gives excellent staining results with Giemsa or Wright stain For the information of those who have not followed the variations in staining characteristics of blood cells with changes in the reaction of the water we call attention to the following points regarding the appearances of blood cells where the water is either acid or alkaline

If the water is acid the erythrocytes become a bright red orange instead of light yellowish orange and the white cells are almost indistinguishable All eosin stains become very bright reddish orange The eosinophiles stand out particularly brilliantly In a count of eosinophiles alone it is advisable to use slightly acidified water The nuclei of all cells will stain a pale sky blue The cytoplasm of all lymphocytes and monocytes is very pale blue or invisible The cells types can not be definitely differentiated from each other if the water is acid The neutrophile cells become extremely pale their nuclei stain either pale blue or pale lavender and the cytoplasm stains a definite pink but no granules are visible The age of the various neutrophiles cannot be determined accurately because of the indefinite staining of the nuclei Blood platelets are pale Malaria parasites lose much of their color the red chromatin stains paler and the blue cytoplasm is scarcely visible which makes identification extremely difficult

With alkaline water the erythrocytes stain blue or green but a purple cast is imparted to all blues and particularly to the cytoplasms of the lymphocytes and monocytes The cytoplasm of the lymphocytes may be grayish or lavender and that of the monocytes may be deep lilac pink or lavender or even purple while the cytoplasm of neutrophiles becomes deep lavender or almost red Eosinophiles with alkaline staining show deep gray or blue granules instead of the dull orange appearance that is obtained when neutral water is used The granules of eosinophiles stain this peculiar color when the water is stale) The granules of all the neutrophiles become overstained or overstained so that they not only appear more numerous but also larger than normal This makes detection of toxic granules impossible Chromatin granules of all nuclei assume the appearance of large black lumps and the nuclei and the nuclear wall seems broken Nucleoli are usually not distinguishable Erythrocytes with alkaline water not only change in staining characteristics but also appear to have no center Frequently the edges seem to have horny projections and the cells look crenated Most leucocytes look frayed at the edges Malarial parasites stain particularly well with slightly alkalinized water but if the water is too alkaline it is impossible to differentiate the chromatin from the cytoplasm Blood platelets with alkaline water stain well and stain red or lavender One cannot identify them by their structure but only by their size and arrangement

Another danger in staining blood films is in using too little of the staining solution or in overwashing Water will decolorize the stain if left in contact with the slide For this reason we suggest that slides be washed rather slightly then allowed to stand on end to dry so that the excess water may drain off instead of removing the color In staining the slides should be placed on a staining bridge over a staining pan and as much diluted stain as the pan can accommodate should be used If slides are understained or overwashed the true color will be lost the nuclei and cytoplasm will blend instead of being distinct and most of the cells will look very fragile Understained cells appear very much like cells stained with acid water

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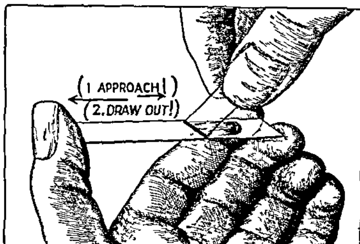


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Diluting the Stain Dilute only as much Giemsa stain as needed for the work at hand While stock Giemsa *stain is stable and does not precipitate*, diluted Giemsa stain will change within an hour or two

Measure the quantity of distilled water needed to stain the slides, placing it in a flask or cylinder Add 1 drop of Giemsa stain for each cubic centimeter of neutral water, shaking very slightly during *the addition of each drop Do not add all the Giemsa stain* at once, and do not shake vigorously, or a precipitate will form Shake only enough to ensure a good mixture of the stain and the water The drop should be measured with a dropper the opening of which is not too small

If a dropping bottle is used as a container for Giemsa stain, it must be prepared by allowing neutral distilled water to stand in contact with the glass for at least a week, changing the water each day The bottle must be dried before the Giemsa stain is placed in the bottle

Fixing the Film Absolutely pure, acetone free methyl alcohol should be used We recommend that made by the National Aniline and Chemical Company, New York

The methyl alcohol should be kept in a Koplin jar for use and at the end of the day transferred to a bottle and kept tightly stoppered to prevent evaporation

For fixation, place the slides in methyl alcohol for 3 to 5 minutes Fresh films should be fixed 5 minutes, films which have been kept for several days require only 3 minutes' fixation Remove, allow to dry in the air, and stain

Staining the Film Place the fixed slides on a staining bridge and flood with diluted Giemsa stain Allow the stain to remain on the slide for 30 minutes or in some cases 45 minutes, wash with neutral distilled water, and stand in a vertical position to dry Do not overwash If the slides are too blue, rewash and allow to dry

Changes in Giemsa Staining to Bring Out Special Structures

(a) *Malaria*—The water should be slightly alkaline Use 1 drop of 1% sodium or potassium carbonate solution to each 25 c c of neutral distilled water before adding the Giemsa stain (1 drop of stain for each cubic centimeter of water)

(b) *For Eosinophiles—Allow the distilled water to remain slightly* acid to bring out the granules of the eosinophiles

(c) *For Spirochetes*—Alkalinize the stain by adding 1 drop of 1% potassium carbonate solution to each 10 c c of distilled water before diluting the stain

Fix the film Allow to dry Flood with diluted Giemsa stain (alkalinized), and steam gently for about 10 minutes, or stain cold for 24 hours (in a Koplin jar)

Wash in running tap water for 3 minutes and dry

Spirochetes are red, other organisms are blue

(2) **Rapid Giemsa Stain *(For Emergency Use Only)***.—*The method is that of* McGee (1932) Stain for ½ minute with a mixture of 20 drops of methyl alcohol and 10 drops of Giemsa stain (mixed in a dry tube and poured over the slide) Add an equal volume of *neutral distilled water and allow the mixture to remain on the slide for 2 minutes* Flood *off the stain with neutral distilled water, dry, and examine*

(3) **Wright Staining**—No fixative is necessary since the stain contains methyl alcohol The length of time for staining may vary with different batches of stain

Flood the slide with the Wright stain and allow it to remain for 1 minute Add neutral distilled water *until there is a mixture of equal parts of stain and water* and allow the mixture to remain on the slide for 3 or 4 minutes Flood off the stain, dry the back of the slide to remove excess stain, and stand in a vertical position until dry

(4) **Wright Stain Modified by Bercovitz (1934)** —

Fill a staining jar with pure *methyl alcohol*

Fill a second jar with 30% Wright stain

Immerse the blood film in the methyl alcohol for 5 minutes

Place in the stain for 2 minutes or longer, depending on the depth of staining desired *Wash the slide as usual*

The stain can be used repeatedly. If the fluid level decreases add more diluted stain until there is enough to cover the slides. Slides left in the methyl alcohol for an hour or more showed no changes in the staining characteristics of the cells.

(5) **The May-Grünwald-Giemsa or the Wright-Giemsa Staining of Blood Films and Bone Marrow.**—Stain with Wright stain or May-Grünwald stain in the usual manner, and wash.

Dry in the air, then stain for 30 minutes with dilute Giemsa stain. Wash with neutral distilled water and allow to dry.

This method is particularly recommended for staining bone marrow preparations.

Making and Staining Thick Drop Preparations

The thick drop method of examination of blood is a very important procedure in searching for parasites and detecting polychromasia and for counting eosinophiles. Parasites of malaria, filariasis, trypanosomiasis, etc., may be found more readily in the thick drop than in the blood film, for the thick drop represents a concentration of the blood of about 50 times that of a film. The erythrocytes are dissolved by the water in the diluted Giemsa stain or by a dehemoglobinizing solution, thus making it very easy to see either the blood parasites or the reticulated structures of the young erythrocytes. The eosinophiles are very definite, the granules being very distinct and bunched together. The thick drop preparation manifestly cannot be used for differential counting. All that remains of the erythrocytes is the reticulum of young cells, nuclei when present, and parasites when in the blood; of the neutrophiles only the nuclei and nonsoluble granules remain on the slide; the basophiles appear as a group of red stained fibrin needles around a washed out nucleus.

Technic.—Place 2 drops of blood on a glass slide and spread immediately in a circle to 3 times the original diameter of the drops. Allow to dry thoroughly at room temperature or for ½ to 3 hours in a bacteriologic incubator at 37° C. Keep the slides out of bright sunlight, away *from flies and other insects and protect from dust*. DO NOT FIX.

Place the slide on a staining bridge and cover very gently with dilute Giemsa stain (1 drop of stain for each cubic centimeter of neutral distilled water), taking care not to loosen the drop from the slide.

Allow the stain to remain for 3 minutes or until the blood is dehemoglobinized and tilt the slide and allow the stain to run off. Again cover with dilute Giemsa stain and stain for 30 minutes. Wash gently but thoroughly with neutral distilled water and dry in the air in a vertical position. Examine under oil immersion objective.

Modified Method of Staining Thick Drops for Examination for Malarial Parasites (Vigo, cited by Gradwohl, 1948).—Mix Giemsa stain with buffer solution pH 7.0 to 7.2 or neutral distilled water in the proportion of 1 drop of stain for each 2 drops of buffer solution. Mix in a test tube or small graduate.

Place just enough stain on the thick drop to cover it and allow to remain for 3 minutes.

Wash either by immersing in a jar of neutral distilled water or in the usual manner of washing a slide.

Rapid Thick Drop Staining Method (Field, 1941).—Make a thick film about the size of a shilling or a quarter dollar, about 10 to 15 times the thickness of an ordinary thin film. It should be thick enough so as barely to read the dial of a watch through the film. Stain as soon as it has dried. Drying may be accelerated by a hot air current from an ordinary hair dryer. No fixation is used. Freshly prepared films stain better than those several days old.

Solution A

Methylene blue	0.8 Gm	
Azur I	0.5 Gm	(American equivalent is Azur B)
Na_2HPO_4, anhydrous	5.0 Gm	
KH_2PO_4, anhydrous	6.25 Gm	
Distilled water	*500* cc	

Dissolve the phosphate salts first. Effect solution of the dyes by grinding in a mortar, using a small amount of the phosphate solvent at a time. Allow to stand for 24 hours *and filter. If Azur I is not obtainable*, good results are secured by mixing methylene blue from medicinal methylene blue and a buffer as follows. Dissolve 1.3 Gm medicinal methylene blue and 5 Gm anhydrous Na_2HPO_4 in 50 cc of distilled water. Bring to a boil. Evaporate on a water bath almost to dryness. Add 6.25 Gm anhydrous KH_2PO_4. *Add 500* cc distilled water, stir until stain is completely dissolved, and set aside for 24 hours. Filter before use.

Solution B

Eosin (yellowish, water soluble)	1.0 Gm
Na_2HPO_4, anhydrous	5.0 Gm
KH_2PO_4, anhydrous	6.25 Gm
Distilled water	500 cc

Follow directions for making solution A.

If a scum appears on either of these 2 solutions, filter again. The same solution may be used for weeks without deterioration. The eosin solution should be removed when a greenish color appears which is due to the carrying over of the methylene blue. Keep the stain in covered jars, at a depth of about 3 inches. Maintain this level by adding more stain from time to time.

Staining Method

Dip into solution A for 1 second.

Rinse by "waving" in water for a few seconds until no more stain comes off.

Dip into solution B for 1 second.

Rinse by gently "waving" in water for 2 or 3 seconds.

Place vertically in rack to dry.

Staining of parasites is optimal at the lower edge of the film toward which the hemoglobin has drained.

Colors

General ground. Creamy yellow color, sometimes uniform, sometimes mottled with pale blue.

Leucocytes. Nuclei, deep blue, sharply defined, cytoplasm, pale blue, vaguely defined, granules—eosinophilic, large, red, well defined, neutrophilic, small, pale purple, vague.

Malarial parasites. Cytoplasm, blue, chromatin, dark purplish red, pigment, unstained, yellowish of varying shades.

Thick Film Method of Barber and Komp for Malaria (1929) —

Slides should be clean and fat free and should not be fogged or scratched.

Make a thick smear of blood by placing 4 small drops of blood on a slide and spreading *it to about 2 cm in diameter. Preparations must not be too thin.*

Allow to dry thoroughly in the air in a horizontal position (1 or 2 hours).

In surveys for malarial parasite carriers, hundreds of preparations must be examined. Carry out the technic in groups of 25 slides as follows.

Smears must be at least 1 cm from the end of the slides.

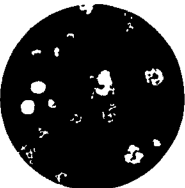
Labels are placed at the other end of the slides.



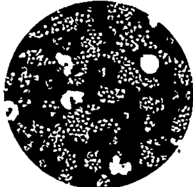
NORMAL THICK DROP
X 950



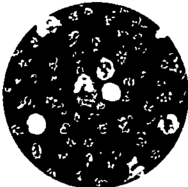
LEAD POISONING
X 950



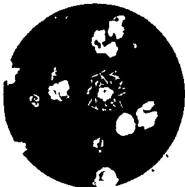
FATAL FALCIPARUM MALARIA
X 950



VIVAX MALARIA
X 950



FILARIASIS
HEMATOXYLIN-GIEMSA STAIN



TRYPANOSOMIASIS GAMBIENSE
X 950

Place the slides in a box and insert between the labeled ends blocks of cardboard separators 1/16 to 1/4 inch thick and 1 1/4 inches long assemble the slides and cardboard separators and fasten them together with a stout rubber band The entire group may be stained as a single unit

Dilute Giemsa stain with distilled water immediately before use The pH of the water should be between 7 0 and 7 2 Use 1 drop of Giemsa stain for each cubic centimeter of neutral distilled water, shaking the mixture slightly after the addition of each drop Do not shake too vigorously or a precipitate will form

Immerse the slides in a vertical position in a staining dish containing the diluted Giemsa stain There should be enough stain to cover the preparations but it must not interfere with the labels Stain for 30 minutes to 1 hour depending on the degree of stain desired. Discard the diluted stain

Rinse gently with neutral distilled water If the slides are overstained rinse for 3 to 5 minutes in water

Allow to dry in the air and examine with the oil immersion objective

Staining Thick Drops With Wright Stain —Prepare the thick drop in the usual manner and allow to dry thoroughly Place in a solution of 2 [illegible] formalin and [illegible] acid and let the preparation dehemoglobinize for 2 or 3 minutes Neutralize [illegible] carbonate solution Stain as usual with Wright stain

Examination of the Thick Drop

Examine with the oil immersion objective Polychrom[illegible] structures stained blue Basophilic punctation appears as [illegible] circle Orthochromatic erythrocytes dissolve Parasites an[illegible]

Bone Marrow Studies

Bone marrow studies are now an essential part of [illegible] In all uncertain cases of blood diagnosis it is well to [illegible] diagnostic examination This may be procured in various ways W[illegible] mend the Turkel technic for biopsies of the sternum

The advantages of this method are that it is easily and rapidly performed at bedside or office and does not leave a disfiguring scar It controls the depth and force of penetration, in other words it prevents penetration of posterior lamella and mediastinum There is no dilution of marrow with circulating blood There is preservation of marrow topography The biopsy by this method shows cells adherent to the marrow wall which are not seen by aspiration Further, the biopsy shows the true proportion of cells in marrow or the myeloid erythroblast ratio It checks results of treatments quantitatively It possesses the advantage that aspiration and infusion may be performed through the same aperture

Technic (Turkel, cited by Gradwohl, 1948) —Cleanse the skin over the desired site usually opposite the third rib with surgical antiseptic Infiltrate skin subcutaneous tissue and periosteum with local anesthetic

Insert outer needle with stylet in place with the tip of the needle in the direction of the face of the patient at an angle of about 45 degrees through the skin subcutaneous tissue and periosteum until the tip just engages the anterior lamella of the sternum

Leave the outer needle in place and remove the stylet

Insert the trephine needle with stylet into the outer needle

Remove stylet of inner trephine needle

While holding the outer needle with the fingers of the left hand, turn the h the trephine needle with the fingers of the right hand, with a slight clockwise c clockwise motion, at the same time exerting gentle inward pressure A sudden of resistance signifies entrance of the trephine tip into the sternal cavity *The clo counterclockwise motion with slight pressure, should continue until the neck of the needle is completely within the head of the outer needle* Rotate the head of the inner in order to detach the plug from the surrounding marrow

(a) **For Aspiration** While holding the knurled handle of the inner needle *the* outer needle into the sternum about 6 mm until the neck of the inner needle be completely visible Remove the inner needle Attach the syringe and aspirate about of blood marrow mixture Remove syringe and express mixture immediately into ox tube

(b) **For Biopsy** Remove the inner needle and with its stylet force the marrow into a bottle containing a fixative or use it as imprint *or smear Insert stylet into* needle, remove outer needle, and cover the point of insertion with antiseptic dressi

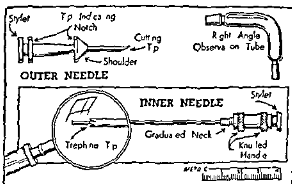


Fig 461 —The Turkel needle for aspiration or biopsy of the sternum

Iliac Crest in Bone Marrow Punctures

Rubinstein (1947) stated that *bone marrow can be obtained easily* safely from iliac crest and may at times provide information not obtair from sternal aspiration His method follows

The site for the iliac crest puncture is chosen on the crest over an area within posterior to the anterior superior iliac spine on either side of the body According t thickness of the tegument, a needle, 1 inch to 2½ inches long 16 gauge, and furn with a stylet is used for puncture a 20 cm tightly fitted dry syringe is used for aspira

The determined site is prepared with iodine and alcohol and infiltrated with cent novocain solution until the periosteum is reached, the periosteal space is then inj very slowly, usually no more than 2 c c of the novocain solution is required The pa lies in the supine position, in cases of very pronounced abdominal distention (as enlarged viscera) the patient is tilted on his side The puncture is performed with needle at a 45 degree angle to the long axis of the body and with pressure applied by palm of the hand The aspirating needle is forced into the bone with steady pre and slight rotation A distinct "give" sensation is usually felt when the needle e the medullary cavity As the needle is firmly embedded in the medullary cavity, stylet is withdrawn and the syringe attached to the needle In order to avoid admix of blood, the plunger is slowly withdrawn until the first drop of marrow fluid is served in the capillary end of the syringe Bone marrow aspiration is accompanied l slight sensation of pain (suction pain)

The material removed may be used in the usual way for enumeration of total

Examination of Bone Marrow Preparations

Touch preparations are made on the surfaces of clean fat free glass slides A few smears are also made

The best method of *staining is the combination of Wright and Giemsa stains given earlier in the chapter*

Supravital Staining of Erythrocytes

Supravital staining means staining of cells after their somatic death but before their molecular death has taken place that is to say, after their removal from the living body but before all cellular activity stops Reagents are used which are of low toxicity or are nontoxic to *the cell and which will stain them* in the course of a few minutes

Rapid Supravital Staining Method of Schilling—This does not give permanent *mounts*

The reagent is a 1 per cent alcoholic solution of brilliant cresyl blue filtered after 24 hours

Keep the stain in a glass bottle with a glass rod attached Dip the glass rod into *the stain and spread a thin layer of the stain over the slide Allow to dry*

Place a very small drop of blood on the center of the slide and cover immediately with a thin cover glass Allow to stand for 5 or 10 minutes and examine with the oil immersion objective

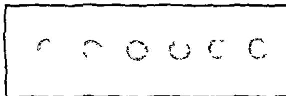


Fig 46? —Bone marrow touch preparation

APPLICATION OF HEMATOLOGIC STUDY TO TROPICAL DISEASES

In respect *to the application of hematologic study to* tropical diseases it is to be noted that certain cells of the organism show activity when invaded by some foreign body living or dead These cells which can act *in situ* (fixed cells) and those which may come from a distance (mobile cells, *for example* leucocytes) have a phagocytic function by which they can encompass into their cytoplasms foreign particles living or dead that have been introduced into the organism This phagocytosis is exercised principally by 2 kinds of cells the polymorphonuclear neutrophiles and the monocytes *or large mono* nuclears Metchnikoff called the first class microphages because they engulfed small particles especially bacteria. The other type he called macrophages These are the monocytes derived from reticuloendothelial structures They usually phagocytize larger elements such as cells erythrocytes *protozoa* etc

The polymorphonuclear neutrophiles or microphages are of *myeloid* origin circulate in the blood and accumulate in foci of *microbic invasion*

(diapedesis) where they degenerate to form pus cells Accumulation of polymorphonuclear neutrophiles in the tissue is one of the histologic signs of an acute inflammation *Relative increase in the blood is called polynucleosis* or neutrophilia and is generally accompanied by an increased total number of leucocytes in the blood (leucocytosis) Leucocytosis with polynucleosis of the blood is therefore constant when there exists in the patient some focus of acute bacterial inflammation especially when there is an evolution toward abscess formation (suppuration)

Monocytes or macrophages originate in the reticuloendothelial system and circulate in the blood *where an increased number (monocytosis) occurs in* certain protozooses such as malaria leishmaniasis etc In some parasitic and protozoal diseases the endothelial cells of the reticulum of all the organs and tissues especially those of the liver and spleen are more or less invaded by parasitic elements (malaria leishmania)

The cytoplasm of these endothelial cells or true macrophages is the habitual localization of many parasitic microorganisms such as leishmania actinomycetes lepra bacilli etc We wonder if this inclusion of parasites in the cytoplasm of the macrophages is due to a true phagocytosis a more acceptable theory or if it is due to attack with parasitic invasion of such cells (Kouri)

The occurrence of eosinophilia is the most frequent observation in helminthic infestations Increase in monocytes is seen in malaria and leishmaniasis Note also that some tropical affections are accompanied by diminution of number of leucocytes in the blood (leucopenia) others show a diminution of total number of erythrocytes (anemia) or an increase in these elements (hyperglobulia)

Cellular Reactions —

Blood eosinophilia local eosinophilia leucopenia with mononucleosis anemia local inflammatory reactions acute subacute and chronic remote reactions such as lymphatic gland enlargements hepatomegaly and splenomegaly changes in the bone marrow hyperplasia metaplasia and neoplasia—these are all cellular reactions on the part of the organism which may be observed in parasitic affections and which in some manner permit one to look upon them as specific for parasitism although they are present in many other nonparasitic affections on the other hand they may not be present in such affections

For example blood eosinophilia which is very frequent and in many cases very high in parasitic diseases especially in those caused by worms may be entirely absent or on the other hand it may be present in cutaneous affections in urticaria in asthma and other allergies which are not parasitic as well as in tuberculosis in Hodgkin s disease in essential eosinophilia etc

It is clear that a blood eosinophilia in a tropical country makes one think of parasitism *and demands an investigation by direct methods for* a definite diagnosis of parasitism Again anemia may be due to many causes Among these is parasitism especially by Necator and Ancylostoma These worms

may cause anemias which may differ from those caused by malarial plasmodia or histolytic amebae An investigation and search for parasites should be made when an anemia is associated with eosinophilia

Mononucleosis is frequently seen in malaria and calls for an investigation directed toward finding this hematozoan or its pigments in blood or in smears from splenic puncture during life and in all the organs and tissues at autopsy

Thus eosinophilia anemia mononucleosis must be considered as cellular reactions of the organism Therefore investigation of these cellular reactions are useful because when present they direct suspicion toward parasitism and lead to the search for the parasites by direct methods for the establishment of a correct diagnosis

From personal observations and from literature studies an alphabetically arranged list of the various tropical diseases with their accompanying blood changes is here presented

African Sleeping Sickness —See Trypanosomiasis

Amebiasis —

There is no blood picture characteristic of amebiasis A microcytic anemia is frequently seen The red count has been recorded as below 4 500 000 in 57 cases out of 89 studied (Hinman and Kampmeier 1937) less than 4 000 000 in 38 of the cases Nine cases showed erythrocyte counts below 3 000 000 The hemoglobin is usually between 65 and 80 per cent at times higher than 80 per cent and some cases show hemoglobin values below 65 per cent In chronic cases of long standing the red count may be 3 000 000 or rarely 2 500 000

In the acute stages the white count is higher than it is in bacillary dysentery In chronic cases without complications it is usually below 12 000 There may be lymphocytosis and a slight monocytosis with eosinophilia of a slight degree in some patients

Amebic Abscess of the Liver —

The leucocytosis varies between 12 000 to 20 000 according to many authors but it may be between 10 000 and 5000 (Felsenfeld) According to Da Silva (1945) the larger the abscess the lower the cell count At times there is an increase in the polymorphonuclear leucocytes Manson Bahr (1936) found the average differential count to be 70 8 per cent polymorphonuclears 22 2 per cent lymphocytes 6 per cent large mononuclears and 1 per cent eosinophiles

With secondary infection of the liver abscess both the fever and the white count are high

Amebic Abscess of the Lung —

There is neutrophilic leucocytosis with white counts of 15 000 to 20 000

Amebic Hepatitis —

There is a leucocytosis of 15 000 to 30 000 with a decrease in the number of mononuclear cells

Amebic Appendicitis.—

There may be an increase in the white count but if the count exceeds 15 000 or 16 000 secondary infection should be suspected

Ancylostomiasis.—See Hookworm Disease

Anemia Achrestic.—

The red count is 2 000 000 to 3 500 000 or less with a hemoglobin of 60 to 70 per cent The color index and volume index are greater than 1 0 There is a hyperplastic megaloblastic bone marrow (Clerch Rius)

Anemia, Beriberi.—See Beriberi

Anemia Chlorosis.—See Chlorosis

Anemia Hypochromic of Children.—

There is a hypochromic anemia similar to that in the adult with hyper leucocytosis and lymphocytosis (large lymphocytes)

Anemia, Hypochromic, Idiopathic.—

The red count varies between 3 000 000 and 4 100 000 the hemoglobin be low 50 per cent at times as low as 30 per cent Erythrocytes are small and hypochromic the cell diameters being about 6 2 to 6 7 microns The mean corpuscular volume is less than normal and the color index about 0 62 The reticulocyte count is normal There is no change in the blood platelet or the differential counts Normoblasts may be present

Anemia Hypochromic, of Pregnancy.—

The red count is 3 500 000 to 4 200 000 with hemoglobin values of 35 to 40 per cent or perhaps as high as 50 per cent The erythrocytes are small and hypochromic and there are poikilocytes The reticulocyte count is somewhat diminished There is leucocytosis and slight neutrophilia (70 to 75 per cent)

Anemia, Myxedema.—

The red count varies from 3 000 000 to 4 000 000 with hemoglobin percentage *of 50 to 60 per cent without signs of regeneration in the circulating* blood The hemoglobin may be as low as 40 per cent

Anemia, Nutritional Iron Deficiency.—

The iron deficiency anemias are chlorosis idiopathic hypochromic anemias hypochromic anemias of childhood and hypochromic anemias of pregnancy See under separate headings

Anemia, Nutritional, Macrocytic.—

Although very low red counts (below 1 000 000) have been recorded the majority of cases show erythrocyte counts of 2 000 000 or slightly lower with hemoglobin decreasing proportionately in most cases The mean corpuscular hemoglobin concentration varies between 33 and 37 per cent so that the anemia is usually normochromic The erythrocytes are macrocytic between 100 and 150 cubic microns The Price Jones curve is shifted to the right but

tends to retain its normal shape and is not usually a low spread out curve like that in pernicious anemia There is usually polychromasia and anisocytosis but to a slight degree Normoblasts are sometimes found but not megaloblasts Reticulocyte counts are about 5 per cent in the hemolytic form and about 1 or 2 per cent in the other forms

The white count is usually normal or slightly increased There may be a slight relative lymphocytosis

There are no true hemoglobinized megaloblasts in the bone marrow but the young basophilic primitive red cells without hemoglobin and with finely stippled highly staining nuclei (often referred to as megaloblasts) are considerably increased in numbers

Anemia, Nutritional Macrocytic, Due to Deficient Absorption of the Pernicious Anemia Factor —

The red count is usually about 3 000 000 to 4 100 000 with hemoglobin values of 70 to 75 per cent The white count is 6 000 to 8 000 per cubic millimeter

Anemia, Nutritional, Macrocytic, Due to Deficiency of the Antianemia Principle or Pernicious Anemia Factor —

The red count is usually below 2 000 000 and may be as low as 500 000 (Clerch Rius) The hemoglobin is not lowered proportionately to the erythrocytes and may be 50 to 70 or 75 per cent The color index is above 1 0, usually between 1 30 and 1 50 or more The mean corpuscular hemoglobin concentration is more than 30 μg The red cell diameter is 8 5 to 9 microns The mean corpuscular volume is more than 94 cubic microns about 110 to 130 cubic microns Volume index is above 1 0 usually about 1 15 to 1 60 This is a macrocytic hyperchromic anemia

There is anisocytosis and macrocytosis with the Price-Jones curve flat Normoblasts erythroblasts and erythrocytic nuclear remnants are found Cabot ring bodies and Howell-Jolly bodies are often present The diagnostic elements are the megalocytes and megaloblasts

The white count is low between 2 000 and 4 000 When the count is low, the disease is serious when it begins to rise there is remission and good response to treatment Neutrophile count is 30 to 40 per cent or more (neutropenia) with an eosinophilia and absence of basophiles lymphocytosis of 40 to 60 per cent or higher The monocyte count is low about 0 1 per cent Myelocytes have been reported in some cases 0 5 to 1 5 per cent The blood platelet count is low but not below 40 000

The bone marrow is megaloblastic There is increased hemolysis with increase of bilirubin in the blood and urobilin in the urine

Anemia, Pellagra —See Pellagra

Anemia, Pernicious of Pregnancy —

The red blood cell picture is the same as that in pernicious anemia but the white picture shows leucocytosis and neutrophilia

Amebic Appendicitis —

There may be an increase in the white count but if the count exceeds 15 000 or 16 000 secondary infection should be suspected

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The bone marrow is megaloblastic There is increased hemolysis with increase of bilirubin in the blood and urobilin in the urine

Anemia Pellagra —See Pellagra

Anemia, Pernicious of Pregnancy —

The red blood cell picture is the same as that in pernicious anemia but the white picture shows leucocytosis and neutrophilia

Anemia, Scurvy—See Scurvy

Anemia Sprue—See Sprue

Anemia, Vitamin C Deficiency—

See also Scurvy

The red count varies from 3 000 000 to 4 200 000 or less some cases having counts of only 1 000 000 The hemoglobin is from 60 to 75 per cent but it has been reported as low as 40 to 50 per cent Normoblasts as well as increased reticulocyte counts may be found There is no change in the white count or in the blood platelets *At times there is a slight decrease in the counts of* each but not excessive Bleeding time clotting time and clot retraction are normal

Balantidiasis—

Uncomplicated cases show essentially normal blood pictures

Bartonellosis—

(1) **Oroya Fever**—There is a very rapid progressive severe anemia from the beginning of the disease The red count is commonly as low as 1 000 000 or even less within 3 to 5 days of the onset of the disease although these figures are more often seen at the end of 1 or 2 weeks Sometimes there may be a loss of as many as 300 000 erythrocytes per cubic millimeter of blood in 24 hours The hemoglobin may be reduced to as low as 20 to 30 per cent within 2 weeks The color index is often above 1 0 Probably no other condition but hemorrhage produces such a rapid fall in the erythrocyte and hemoglobin figures The volume diameter and thickness of the red cells are greater than normal The mean corpuscular hemoglobin concentration is often low but it may be normal The blood volume is increased especially when the anemia is very pronounced The anemia is often macrocytic with anisocytosis and poikilocytosis quite marked Large numbers of reticulocytes and normoblasts are found in the circulating blood and at times megaloblasts and all the bizarre types of cells which are seen in pernicious anemia are observed in *the circulating* blood

There are as a rule large numbers of Bartonellae in the red cells the number varying Sometimes 99 per cent of the erythrocytes are infected (Groot) and it is possible to find 10 to 15 organisms in a single cell but only in extreme cases Polychromatic erythrocytes and macrocytes are less infected, and only in exceptional cases with a very high degree of parasitism are *the microorganisms found in normoblasts Bartonellae may at times be* seen in the cytoplasm of monocytes

The bone marrow is hyperplastic megaloblastic

Leucopenia may be observed at the beginning of the disease although in *uncomplicated cases the number of leucocytes is customarily normal* (Hurtado 1938 cited by Groot) According to some authors the leucocyte count is increased and may be as high as 20 000

There is no typical differential count although it is possible to find either a very slight lymphocytosis or more commonly an increase in the polymorpho

nuclear cells Juveniles are quite common The eosinophiles disappear and myelocytes and myeloblasts may be present

The sedimentation rate is greatly accelerated with rates of 100 and 172 millimeters in 1 hour with the Westergren method The formol gel test is sometimes positive as well as the flocculation of serum globulin with distilled water (Groot Mayoral and Martinez 1941 cited by Groot) Autoagglutination is rare but sometimes occurs

(2) **Verruga Peruana or Benign Type** —There is a simple anemia

Beriberi —

According to Napier (1940) there is often a marked macrocytic anemia which may respond to thiamin chloride injections The lymphocytes are below normal and in the infantile form small lymphocytes may be absent

Blackwater Fever —See Malaria Blackwater Fever

Blackwidow Spider Bite —

The white count is slightly elevated and there is a slight neutrophilia

Blastomycosis, South American —

The blood picture is characteristic of infections in the advanced cases with leucocytosis neutrophilia rarely eosinophilia anemia and accelerated sedimentation rate The sedimentation rate increases as the case develops decreases and returns to normal with regression of the lesions There are no changes in the blood at the beginning of the disease

Blood Dyscrasias Due to Arsenical Drugs —

Three types have been recognized thrombocytopenia granulocytopenia and aplastic anemia

Bothriocephalic Anemia —See Diphyllobothrium Anemia

Brucellosis —

Mild anemia of the macrocytic hyperchromic type is present The anemia is related to the general status of the patient especially with respect to the intensity and persistence of the febrile reaction Red cell counts as low as 3 000 000 have been recorded but the count is seldom below 2 000 000 in uncomplicated cases

In acute brucellosis there is leucopenia In chronic brucellosis there is either leucopenia moderate leucocytosis or normal leucocyte counts Lymphocytosis is a striking and constant feature of the blood picture in all of the manifestations of brucellosis This is true in both percentage values and in absolute numbers of lymphocytes and there is an unusually high proportion of immature lymphocytes The polymorphonuclear leucocytes may be reduced in absolute numbers with increase in monocytes

There are no characteristic changes of diagnostic importance in the morphology and other characteristics of the white and red blood cells although a marked stab shift is usually noted

The sedimentation rate is usually not high except when regional complications are present

Chagas Disease or Schizotrypanosis —

(1) **Chagas' Disease** —Diagnosis by laboratory methods is based on finding the trypanosome in the blood by direct examination of fresh blood between cover glass and slide This examination is particularly advised when the disease *occurs in nursing infants for the number of parasites found in the* circulating blood is quite high The thick film examination is of greater value in examining the blood of older children and adults The examination should be repeated periodically or every day

A high monocytosis is suspicious of this disease and as a rule *consistent lymphocytosis* with hypoeosinophilia The return of the eosinophiles to the blood picture is a sign that the patient is improving

(2) **Chagomas of Inoculation** —*In children there is a high monocytosis* at other ages there is a very high lymphocytosis accompanied by a more or less marked eosinophilia This may occur in the first stage or primary period (Mazza)

Chlorosis —

The red count is 3 500 000 to 4 000 000 with hemoglobin from 35 to 40 per cent or up to 50 per cent There is marked anisocytosis poikilocytosis and microcytosis with great increase in reticulocytes The color index is very low between 0 4 to 0 7 There is marked polychromasia and at times basophilic punctation in the stained film The ratio of plasma to erythrocytic volume is increased (low hematocrit) with increase in the total blood volume The blood platelets are greatly increased in number Lymphocytosis is commonly found although the white count is not characteristically high

Cholera —

Due to the great loss of fluid from the blood vessels and tissues of the body (hemoconcentration) the red count and hemoglobin are very high The *red cell count may* be increased to 7 000 000 or 8 000 000 The white count may be as high as 15 000 to 30 000 rarely 50 000 The monocytes are increased but there is a decrease in the number of lymphocytes There is an increase in the specific gravity of the blood—1 060 to 1 065 The alkalinity is lowered

Chromoblastomycosis —

There is no characteristic blood picture or any hematologic change due to the presence of the fungus in the tissues

Coccidioidal Granuloma —

There is a moderate leucocytosis around 15 000 Eosinophiles are sometimes above normal *There is a secondary anemia*

Colorado Tick Fever —

There is a markedly reduced white blood cell count with a shift to the left of the neutrophiles The blood picture is similar to that of dengue

Beginning with the onset of symptoms there is a progressive decrease in the number of leucocytes which usually reaches the lowest point at the begin

ning of the second attack Typically the white blood cell count falls to between 2 000 and 3 000 per cubic millimeter although one as low as 1 200 has been recorded (Florio Stewart and Murrage 1944) All of the leucocytes are reduced in absolute numbers except the monocytes There is a definite shift to the left in the neutrophiles It is common for the stab cells to outnumber the segmented forms when the count is lowest Four to seven days following clinical recovery the white blood cell count and the differential count have returned to normal

Cysticercosis —

Not much importance has been attached to the eosinophilia since it is found in only approximately 10 per cent of the cases

Dengue —

Dengue does not cause anemia The red count is usually normal decreasing at most to 4 500 000 on the fifth or sixth day There may be mild hematoxic signs such as anisocytosis and poikilocytosis The hemoglobin and color index remain normal

One of the most constant features is the marked leucopenia The count varies between 1 000 and 4 000 on the fifth day although in most cases it is not below 3 000 Cases have been observed with counts as high as 5 000

There is a relative monocytosis which may be as high as 14 per cent The differential count is characterized by a marked left shift with juveniles and stabs increased beginning on the third day The eosinophiles are decreased but increase during convalescence The differential count and the white count return to normal during convalescence No pathologic white blood cells have ever been observed in the blood stream

The blood picture is characterized by constant leucopenia early and marked reduction in the number of segmented neutrophiles increase in small lymphocytes gradual increase in the number of large lymphocytes slight increase in eosinophiles during convalescence

Dermatomycosis —

The blood often shows marked eosinophilia The eosinophilia is marked in chronic cases and anemia may be present

Diphyllobothrium Anemia —

Not all patients who harbor the worm show a severe anemia The anemia is severe in those cases in which it develops The red blood cell count usually decreases to 2 000 000 at times to 500 000 or less Hemoglobin is also low The color index is usually normal or it may vary from 0 94 to 1 34 There is marked anisocytosis with microcytes as small as 3 7 microns and macrocytes up to 16 microns Poikilocytosis with presence of normoblasts and megaloblasts and a reduction in the number of blood platelets is noted There usually is leucopenia with lymphocytosis and very rarely eosinophilia The red blood cells have a slight tendency toward clumping In some cases the anemia may be indistinguishable from pernicious anemia

Histoplasmosis —

In septicemic infections, the number of both red and white cells is decreased. In generalized infections, the bone marrow is almost invariably involved.

Hookworm Disease (Ancylostomiasis and Necatoriasis) —

Hookworm disease is accompanied by anemia which may reach the most severe stages quickly, but in other instances slowly. Usually it appears within 10 to 20 weeks after infection.

It has been estimated that for each 12 worms there is a decrease of 1 per cent in the hemoglobin, thus 240 worms will cause 20 per cent reduction, or, in other words, the hemoglobin will drop from 95 to 75 per cent. A thousand worms will reduce the hemoglobin to approximately 15 per cent. Kouri has noted that cases with more than 1,000 Necators usually show hemoglobin values as low *as 12 to 15 per cent, less than 1,000,000 erythrocytes, and generalized edema.*

The anemia seems to be caused by chronic loss of blood, frequently associated with an iron deficiency, or a state of chronic malnutrition. It has been estimated that about 0.67 c.c. of blood is extracted daily by each worm that has recently been implanted in the human intestine. After several months or years it is possible that *Necator americanus* does not extract more than 0.2 to 0.5 c.c. of blood daily. After the parasite has left the original site of implantation *to attach itself to another more healthy portion of the intestinal mucosa* the blood still flows for some time from the abandoned lesion. If this 0.67 c.c. quantity of blood extracted daily by a single parasite is multiplied by the thousands of worms which may be present, and repeated day after day over a long period of time, it is easy to understand the mechanism by which secondary anemias, so frequently seen in hookworm disease, are produced. If parasitized individuals are well nourished and if liver extracts, iron and vitamins are administered in large enough quantities, no anemia occurs *(Gradwohl and Kourí 1948)*.

In advanced stages, the number of erythrocytes may be less than 1,000,000 and the hemoglobin content may be as low as 17 per cent or less. There are, however, some cases with hyperglobulia and high hemoglobin percentage perhaps due to stimulation of the hematopoietic organs by the hematoxins absorbed.

Three types or stages of blood changes have been observed in hookworm anemia: (1) where the bone marrow is able to maintain the equilibrium *between blood loss and production, and there is no manifest anemia*, (2) where the production is unable to counterbalance the blood loss and a hypochromic anemia results, (3) where the bone marrow is exhausted and aplastic anemia develops.

In the first type, there is eosinophilia and reticulocytosis in the peripheral blood, and despite a continuous loss of blood, increased cell production in the bone marrow is sufficient to maintain equilibrium between blood formation and blood loss, so that in the early stage of the disease, real anemia does not develop if food and living conditions are adequate.

The second type shows anemia microcytosis hypochromia eosinophilia and reticulocytosis in the peripheral blood and eosinophilia and marked erythropoietic activity of the bone marrow

The third type is characterized by severe anemia with the erythropoietic activity of the bone marrow almost nil *There is so called panmyelophthisis* with low cell count relative lymphocytosis and lack of erythropoietic granulocytopoietic and thrombocytopoietic activity of the bone marrow

Hookworm anemia usually shows at the onset a leucocytosis of 17 000 per cubic millimeter with eosinophilia predominating The leucocyte count later drops to normal or below normal with a moderate eosinophilia which remains high for some months In severe cases there is usually total absence of eosinophiles (aneosinophilia)

Infantile Cirrhosis of the Liver (Chaudhuri, R N) —

There is a very distinct microcytic anemia and a pronounced leucocytosis between 15 000 and 20 000 with normal differential count

Infectious Jaundice —See Weil s Disease

Kala-Azar —See Leishmaniasis

Leishmaniasis —

(1) **American** —There is a marked increase in large mononuclear cells

(2) **Cutaneous** —There is usually no diminution in the red blood cell count There is a slight increase in mononuclear cells (monocytes and lymphocytes) in some cases more marked if the blood specimen is taken from the area or near it where the lesion exists In nonulcerative cutaneous leishmaniasis in the Sudan the blood has usually shown leucopenia and eosinophilia In Brazil Mazza and Nino reported in South American leishmaniasis an average of 41 per cent mononuclear cells of which 36 per cent were lymphocytes In blood taken from the region of the sore there were 45 lymphocytes and 3 monocytes The peripheral blood showed an average of 6 per cent eosinophiles

(3) **Visceral (Kala-Azar)** —Anemia is seen as a rule only in the latter stages of the disease although some degree of anemia is usually present The red cell count is fairly constantly 3 000 000 it rarely falls below 2 500 000 in less than 6 months from the beginning of the fever The hemoglobin usually falls in proportion to the drop in the red count The erythrocytes in the blood film are usually slightly macrocytic and hyperchromic Nucleated red cells and cells containing nuclear fragments often are present Polychromatic erythrocytes are found and the reticulocyte count is slightly above normal about 2 to 4 per cent The resistance of the red cells to hemolysis in hypotonic saline solutions is decreased

The most characteristic change in the blood picture is the marked leucopenia with decrease in granulocytes There is a high monocytosis The leucocyte count is usually below 4 000 often 3 000 and in cases which have persisted for a month often less than 2 000 A leucocytosis does not necessarily exclude the possibility of kala azar since septic complications may be present which increase the white count and even without complication the white

count may be occasionally above 10 000, according to Napier The normal ratio between leucocytes and erythrocytes is altered, so that, instead of being 1 750 or 1 666, the ratio is often 1 1,000 or 1 1,500

Agranulocytosis has been described in kala azar The decrease in the leucocytes is entirely in the granulocytic elements, which may drop below 1,000 Eosinophiles are often absent and usually are not found in percentages higher than 1 or 2 per cent

There is both an absolute and a relative increase in the large mononuclear cells ⅔ of which are histiocytes There is a marked shift to the left in the differential count The platelet count is usually below 200,000

The sedimentation rate is very much increased, the mean reading with the Westergren method being 68 3 ± 11 2 mm in 77 mixed cases

Examination of the peripheral blood reveals parasites in the leucocytes but when they are scarce the blood must be concentrated (see Chapter 10)

Parasites may also be found in sternal marrow obtained by puncture

Leprosy —

The predominant feature of the blood in leprosy is an anemia Leucocyte counts are not increased, eosinophilia is not common

Loaiasis —

There is frequently marked eosinophilia, from 50 to 70 per cent, according to Villet

Lymphogranuloma Venereum —

The blood changes in this disease are a leucocytosis above 10 000 and a very minor degree of anemia There are neutrophilia, lymphopenia, and monocytopenia in most cases A few cases show a mild eosinophilia, and sometimes but rarely a neutrophilic myelocytosis

Malaria —

Anemia is always present It is caused both by direct destruction of erythrocytes due to the development of the parasites within them and also by toxic influences The blood becomes thin and watery There is oligocytosis, a lowered hemoglobin content, and a lowered color index Polychromasia is usually marked, and coarse basophilic punctation is a frequent blood finding The blood count may fall to 3 000 000 per cubic millimeter The reticulocyte count is markedly increased In cases with severe anemia, normoblasts are found There may be nuclear spheres, marginal granules and other unspecific indicators of anemia Parasites have been observed in polychromatic and stippled erythrocytes and even in normoblasts

When schizogony is completed pigment is released into the blood stream This can be seen in the form of granules in the blood films and in the thick drop This pigment may be found usually in the large monocytes or phagocytes, but we have observed them in all 4 types of neutrophiles (Schilling classification) The pigment is yellow or brown and light refracting It is

usually arranged in characteristic clumps It originates from devoured or phagocytized parasites and is important in detecting malarial infection when no parasites are found

During the pyrexial period there is a leucocytosis with marked regenerative shift neutrophilia and decrease in the number of eosinophiles Following this period during the afebrile period there is leucopenia marked monocytosis and relative lymphocytosis with slight eosinophilia In severe relapsing cases there is a continuous stab shift In chronic cases there are low white counts monocytosis and lymphocytosis The white count rises rapidly but only temporarily shortly after an open or latent attack In this condition parasites are scarce

In clinically suspected malaria where no parasites are found in the blood one is led to the diagnosis of malaria if polychromasia is present as 2 or 3 plus in the thick drop if basophilic punctation is found and if lymphocytes and monocytes are markedly increased especially if quinine has been administered

All varieties of malaria show similar blood pictures but acute falciparum malaria may show a higher neutrophilia with a regenerative shift to myelocytes

Blackwater Fever —

In blackwater fever the red count may drop to 1 500 000 and the hemoglobin to 10 per cent With improvement this is soon followed by a very marked regenerative normoblastic blood picture Upon continuation or onset of new attacks megaloblastic or aregenerative (reverse) blood pictures occur This is an unfavorable symptom Deaths have occurred in blackwater fever due to suppression of erythropoieses Parasites usually disappear temporarily during an attack of blackwater fever

Mycetoma —

In most of the advanced cases there is an increase in the sedimentation rate moderate leucocytosis 10 000 to 12 000 neutrophilia and decrease in the number of red blood cells

Necatoriasis —See Hookworm Disease

Onchocerciasis —

There is a slight anemia and a marked eosinophilia The eosinophile count has been reported as varying from 10 to 40 per cent The eosinophilia decreases when the lesions are disappearing

Oroya Fever —See Bartonellosis

Pellagra Type of Anemia —

The blood may be normal in mild cases There is an anemia in all moderate or severe cases The erythrocyte count varies from 3 000 000 to 4 000 000 with hemoglobin from 50 to 75 per cent The erythrocytes are usually normocytic and hypochromic In hypochromic cases the hemoglobin usually varies from 50 to 60 per cent

Hypoleucocytosis with slight neutropenia and mild eosinophilia have been observed

The blood picture is not characteristic

Phlebotomus Fever or Pappataci Fever —

The most important change in the blood picture is the marked leucopenia the white count varies between 2 500 and 4 000 per cubic millimeter There is a marked stab shift, with lymphocytosis and a decrease in the segmented cells

Plague —

The red cells and hemoglobin show no reduction at the beginning of the disease A moderate secondary anemia may occur in later stages of the disease The leucocyte count may increase as high as 20 000 to 25 000 except in the mildest cases during the first 3 days of the disease and counts up to 40 000 have been reported

There is neutrophilia with a very marked left shift The blood platelets are increased There is a neutrophilia with lymphopenia Plague bacilli may sometimes be present in the blood in such numbers that a simple microscopic examination of a stained specimen suffices for their detection

Psittacosis (or Ornithosis) —

There is no marked change in the blood picture in psittacosis The leucocyte count is usually normal or subnormal Leucopenia is found in only 25 per cent of the patients (Meyer) Leucocytosis occurs late in the acute phase or in early convalescence At the height of the disease there is a distinct left shift with lymphopenia The sedimentation rate is accelerated at the beginning of the disease The blood picture returns to normal with improvement

Ratbite Fever —

(1) **Infection by Spirillum Minus (Sodoku)** — A certain degree of anemia is an almost constant finding It may be marked with a decrease in the hemoglobin The red count decreases In rare cases only is there an increase in the number of red cells

Leucocytosis varies between 10 000 and 20 000 although there are cases with white counts of 40 000 during the febrile periods In afebrile periods the white count may drop as low as 4 000 During the febrile period the white count rises again *This is a fairly regular observation*

The neutrophiles increase as high as 82 per cent There may be a rather high eosinophilia Variations of these counts may be due to other conditions which may be present in some cases

(2) **Streptobacillary Infections Due to Ratbite** —The blood changes are practically the same as in infection by *Spirillum minus* There is a moderate leucocytosis which in some cases may rise, with increase in neutrophiles and eosinophilia

Relapsing Fever (Tropical) —

There is a leucocytosis of about 10 000 to 20 000 during the febrile stage Examination of the blood should be made the first day of fever The leucocytosis is succeeded later by leucopenia There is an increase in the monocyte count and in the febrile period a polynucleosis

Respiratory Scleroma (Rhinoscleroma) —

A leucocytosis has been reported in 10 per cent of the cases and a left shift in 60 per cent Severe anemia seldom occurs The sedimentation rate is sometimes accelerated In the final stages in cases with stenosis emphysema and emaciation anemia and finally cachexia are not infrequently found (Kouwenaar)

Rhinoscleroma —See Respiratory Scleroma

Rhinosporidiosis —

There are no definite changes in the blood picture characteristic of this disease

Rickettsiosis —See under each disease

Rift Valley Fever —

There is usually a leucopenia with particularly a neutropenia The white count may be below 3 000 There are occasional myelocytes and polyblasts with vacuolated nuclei (Findlay)

Rocky Mountain Spotted Fever —

The anemia has been described both as mild and severe with marginal corpuscles There is a leucocytosis of 15 000 to 25 000 which decreases to about 10 000 after a few days

The differential count shows a monocytosis with a decrease in the number of eosinophiles

Salmonellosis —

See also Typhoid Fever

Anemia is not rare in salmonellosis Cases with fever show most commonly a decrease in the number of red blood cells and of hemoglobin The lowest findings are frequently recorded during the third or fourth week of the disease

A slight increase in the number of white blood cells is not unusual in the earliest days of salmonellosis Frequently 8 000 to 11 000 leucocytes are found during this period

Leucopenia is the rule during the later course of febrile salmonellosis There is a decrease in the polymorphonuclear cells with a relative increase in the lymphocytes The number of white blood cells is restored to normal by the end of the sickness

Perforations of the intestine suppurative processes secondary infections and other similar conditions may cause leucocytosis (Felsenfeld)

Schistosomiasis Haematobia —

In infections with *Schistosoma haematobium*, the number of eosinophiles is increased usually to 10 to 50 per cent of the total count The number of neutrophiles lymphocytes and monocytes shows considerable variation

Schistosomiasis Japonica —

Severe anemia is common in the chronic form

In the acute form there is an extreme and progressive eosinophilia as many as 9 to 95 per cent of the leucocytes being eosinophiles, the average count is about 50 The total white count may vary from 9 000 to 30 000 The eosinophilia does not necessarily account for the entire rise in the white count There is little correlation between the severity of the disease and the degree of eosinophilia

Anemia in the course of the acute disease is unusual in well nourished people but common in chronic severe cases

In the chronic disease the eosinophilia decreases and loses its significance in the presence of the many other parasites usually found in endemic areas (Bang)

Schistosomiasis Mansoni —

During the febrile stage there is leucocytosis and eosinophilia

During the intestinal stage some cases with severe anemia have been reported but the percentage of such cases is low There seems to be no definite etiologic connection between the anemia and the schistosomiasis and it is doubtful if anemia can be considered a consistent manifestation

During the visceral stage the eosinophilia usually but not always persists and leucopenia is characteristic

There are however no changes in the blood picture which are characteristic of this disease

Scurvy —

See also Anemia Vitamin C Deficiency

Although anemia is always present in scurvy experimental work has failed to establish this as being due to ascorbic acid deficiency alone The red count in early cases is from 3 000 000 to 4 000 000 and the hemoglobin relatively lower If hemorrhages occur later the red count may be very low One case has been reported with a red count of 557 000 and one with a count of 370 000 Nucleated reds may be present in considerable numbers principally normoblasts but microblasts and megaloblasts have been found In such cases the blood film resembles pernicious anemia except that the color index is low, and the erythrocytes are not typical of macrocytic anemia The white count is often increased but not always Counts of 20 000 to 50 000 have been recorded There is a relative decrease in granulocytes with an increase in large lymphocytes and monocytes Some workers record leucopenia in scurvy

Shigellosis (Bacillary Dysentery) —

(1) **In Adults** —There may be a leucocytosis in the beginning principally in severe cases of as much as 30 000 but the leucocytosis usually does not

rise above 15,000. The white count decreases during the course of the disease and in the later stages there may even be a slight leucopenia. During the acute attacks there may be hemoconcentration with an increase in the red count, but in later stages there is often a distinct anemia. In chronic bacillary dysentery there is very frequently a macrocytic anemia of nutritional origin.

There is a relative increase in polymorphonuclears.

(2) **In Children.**—The majority of the patients show no anemia. This may be due to anhydremia usually seen in the patients. There is neutrophilia with a left shift, with myelocytes in 40 per cent of the cases. There is no eosinophilia or lymphocytosis, but there is found an increase in the plasma cells. Monocytosis as high as 20 per cent is present in a large percentage of the cases. Degenerative changes of the neutrophiles is always present. The bone marrow shows the picture of an infection. The blood count differs in different patients.

Sleeping Sickness, African.—See Trypanosomiasis.

Spotted Fever.—See Rocky Mountain Spotted Fever.

Sprue.—

"We do not know of any means by which the blood of sprue could be distinguished from that of pernicious anemia; moreover, the bone marrow pictures of the two diseases are indistinguishable."—Suarez.

A number of textbooks and manuals have recorded a moderate microcytic anemia in the early stages of the disease, but we have never observed such cases. In the experience of Suarez, a diagnosis of acute sprue in the presence of a hypochromic microcytic anemia rarely proves correct.

The peripheral blood picture in 150 cases gave the following results: erythrocyte count from 690,000 to 4,410,000 with an average of 2,710,000; hemoglobin 2.4 Gm. to 14.8 Gm. with an average of 9.7 Gm., or 16.5 per cent to 102 per cent with an average of 66 per cent; hematocrit 10.5 mm. to 44 mm. with an average of 33.49 mm.; white count 1,550 to 13,000 with an average of 5,280; color index 0.64 to 2.2 with an average of 1.22; volume index 1.0 to 2.3 with an average of 1.39; mean cell volume 89 cubic microns to 220 cubic microns with an average of 123 C; mean cell hemoglobin 26 micrograms to 59 micrograms with an average of 26 C micrograms; mean cell hemoglobin concentration 20 per cent to 4 > per cent with an average of 20 1 per cent.

In 23 cases the color index was below 1.0, in 2 cases as low as 0.70 and 0 C4.

Hypersegmented neutrophiles in increased number have been described. The blood picture is that of a typical hyperchromic macrocytic anemia.

The sternal marrow usually shows a hyperplastic picture with an increase in megaloblasts indistinguishable from pernicious anemia. The typical bone marrow may be modified in as short a time as 24 hours by administration of a potent liver preparation or of folic acid, and the effect may persist for weeks and even months.

For a detailed account of the differential counts on sternal marrow in sprue and also the reticulocyte response to l[illegible]

Strongyloidiasis —

There is usually a moderate secondary anemia There is a slight eosinophilia of about 8 6 per cent occasionally higher At times the eosinophilia is intense and at such times should suggest the possibility of parasitism especially by a worm In severe strongyloidiasis eosinophile counts have been reported as high as 82 6 per cent

Taeniasis —

Eosinophilia is frequent though not constant or specific in parasitism by *Taenia saginata*

Trench Fever —

There is a leucocytosis seldom exceeding 20 000 with polymorphonuclear neutrophilia which increases during the febrile periods to regress later In chronic cases a relative mononucleosis may be seen (Macchiavello)

Trichinosis —

The erythrocyte count may be increased early in the disease as a result of dehydration later there may be a mild anemia The red count seldom falls below 3 000 000

The majority of cases show a definite leucocytosis the count varying from 10 000 to 20 000 although some individuals have a leucopenia The leucocytosis is principally due to an increase in the eosinophiles which in the differential count may be as high as 80 per cent (in 1 case recorded by Gradwohl the percentage was 90) It is the presence of this eosinophilia which often arouses the thought of trichinosis or some other worm disease Many workers feel that there is no definite correlation between the degree of infection and the percentage of eosinophiles others believe that the eosinophilia varies directly with the muscle symptoms The eosinophilia makes its appearance on the seventh or eighth day of infection and progresses rapidly to a peak but frequently exhibits considerable daily variations After the peak is reached in about the fourth or fifth week there is a steady decline over a period of months or even years The peak is usually reached after the most severe symptoms of muscle invasion have passed In severe cases a rapid drop may occur just before fatal termination Eosinophilia is not necessarily solely connected with trichinosis since there is the same finding but usually to a lesser degree in other worm diseases in bronchial asthma burns allergic states myelogenous leucemia scarlatina certain skin diseases liver therapy etc However the presence of an eosinophilia associated with an acute illness characterized by a rise of temperature suborbital edema and evidence of muscle involvement with or without gastrointestinal symptoms is suggestive at least of trichinosis

The neutrophiles may be reduced to as low as 6 per cent the count varying according to the number of eosinophiles The lymphocytes are often reduced but they usually show an increase with the subsidence of the eosinophilia Monocyte counts may show slight fluctuations

Other hematologic findings are relatively normal except for an increase in eosinophilic myelocytes in examination of sternal bone marrow and possibly a prolongation in blood coagulation time. The author has noted a left shift index in a number of cases.

Trichuris Trichiura Infestations.—

Although conditions similar to pernicious anemia in man have been produced in lower animals infested with large numbers of parasites characteristic for each species of animal, cases of severe anemia caused by *Trichuris trichiura* are rare in man. Eosinophilia is not very pronounced.

Trichostrongylus Colubriformis Infestation.—

If a great number of *Trichostrongylus colubriformis* develop in the intestines of man, they can produce a severe secondary anemia.

Tropical Eosinophilia.—

In tropical eosinophilia there is a leucocytosis and high eosinophilia. The eosinophilia may reach 90 per cent and is higher than in any other disease except eosinophilic leucemia. The white blood cell count may be as high as 70 000, with 50 to 80 per cent eosinophiles.

Tropical Macrocytic Anemia.—See Anemia, Nutritional.

Trypanosomiasis, African.—

The blood picture shows secondary anemia, a gradual diminution of the red count and hemoglobin. Normoblasts are sometimes present. The red cells show characteristic rouleaux formation, the so called autoagglutination, a point of considerable diagnostic value. Cold agglutinins have not been found. The white blood cell count is within normal limits in the beginning of the disease, or at times the white count is lowered. Leucocytosis occurs during the later stages of sleeping sickness. There is a relative increase of lymphocytes and of monocytes. At times there is a terminal increase in the polymorphonuclear leucocytes before death.

The thick drop method is used to find the trypanosomes in the blood.

Tsutsugamushi Disease.—See under Typhus.

Tularemia.—

The white count varies from 5 000 to 20 000, with usually a neutrophilia, but the counts are not of diagnostic value. The author found a very marked left nuclear shift, with 1 to 6 juveniles and 21 to 53 stabs, in a number of cases with segmented neutrophiles reduced to 2 to 34 per cent. A mild to moderate degree of secondary anemia is an inconstant finding.

Typhoid Fever.—

See also Salmonellosis.

(1) **In Adults.**—Typhoid fever is characterized by leucopenia down to 3 000 to 5 000 and a left shift. The eosinophiles disappear at the beginning of the disease and do not reappear until the third week of infection. A very few

eosinophiles in the first stage speaks for a mild infection Reappearance of th
eosinophiles in the third stage of typhoid fever is a good prognostic facto
A relatively high neutrophilic percentage is found in the prodromal stage
as the disease becomes more pronounced there is neutropenia with lymphocyt
sis A supervening neutrophilia is indicative of a possible complication e
pecially if there is a regenerative shift A return of lymphocytes or a retr
gression of the shift to the right in the third stage is a favorable symptom

Unfavorable symptoms are a continued leucopenia and an increasing le
shift

The bone marrow shows very few myelocytes and many myeloblasts

(2) **In Children** —In severe forms a moderate anemia of the hypochrom
type frequently develops due to a nutritional deficiency especially when th
diet is not sufficiently balanced and there is diarrhea

At the end of the first week approximately the sixth day the numbe
of leucocytes is between 6 000 and 8 000 occasionally from 4 000 to 5 000 A
increase in the neutrophiles is observed with a left shift the stab count reach
ing a figure of 10 15 or 20 per cent Lymphocytes vary inversely to the neu
trophile count decreasing in number while the eosinophiles disappear fro
the circulation Before the sixth day the hemogram offers no special in
formation except that a slight leucocytosis may be noted at times accompanie
by the presence of an increased number of stabs Leucocytoses have been ob
served in some cases being 16 000 or higher but these were in children wit
pyogenic manifestations such as purulent otitis

The eosinophiles reappear during the final phase of the disease This i
important for a favorable prognosis A few eosinophiles at the beginning o
the disease indicates a light infection

According to Naegeli a disease accompanied by a high fever is neve
typhoid if the eosinophile count is normal almost normal or increased Con
stant or permanent leucocytosis also reveals that the disease is not typhoi
fever *In young patients the white count very often* is not reduced as much
as in adults Mild forms of the disease show slight leucopenia while in sever
cases the leucopenia is marked A slight leucocytosis at the beginning of the
disease *found by certain investigators has been accepted by Naegeli*

The neutrophiles are moderately increased initially later gradually de
creasing with stab cells predominating

Typhus —

(1) **Classical Typhus** —Some changes in the blood picture are produced
by changes in hemoconcentration and are quite variable in accordance with
the dehydration or rehydration of the patient But there are some definite
alterations in the blood picture due to the disease itself There is a moderate
leucocytosis *from normal to* 18 000 or 20 000 but the white count is usually
between 10 000 and 14 000 This leucocytosis usually follows an initial phase
of leucopenia Neutrophilia with marked regenerative shift occurs with 30
per cent or more of juvenile and stab forms Leucocytosis and neutrophilia
rise suddenly toward the end of the disease when there is hypopyrexia

The eosinophiles disappear gradually and irregularly The lymphoc are in inverse ratio to the neutrophiles, but there is both an absolute ar relative increase after the first 7 days, and more at the end of the fel period

The monocytes increase between the eighth and sixteenth days to stitute 15 to 20 per cent of the white cells Irritation and plasma cells appear Myelocytes vary in number, at times being quite numerous Th the "gay" or "variegated" blood picture of Schilling

The blood platelets decrease during the eruption and increase at the of the febrile period Macchiavello believes that the hematology of typ requires further study

(2) **Rural Typhus or Tsutsugamushi Fever or Scrub Typhus**—Anemi exceptional during the disease There is leucopenia with lymphocytosi 40 to 80 per cent with a type of lymphocyte which recalls that seen in fectious mononucleosis Leucopenia is not a constant finding and there even be a leucocytosis up to 20 000

Ulcerative Colitis, Chronic Postdysenteric—

There is no characteristic blood picture There may be a tendency microcytic anemia as a result of repeated blood loss from ulcers or there ma a tendency to a nutritional macrocytic anemia from malabsorption with without dietary restriction Some patients develop a para sprue condit In uncomplicated ulcerative colitis, the hemoglobin may be almost nor There often is a slight leucocytosis

Uncinariasis—See Hookworm Disease

Verruga Peruana—See Bartonellosis

Weil's Disease—

There is a severe anemia The average red cell count in a fatal case below 3,000,000 The blood platelets are markedly reduced Coagulation t increases until it reaches 20 minutes in the usual infection

The leucocyte count varies from 10 000 to 20 000 or higher with a mod ate neutrophilia The icterus index is elevated at times to about 300 diphasic van den Bergh reaction is typical but not constant

Yellow Fever—

Leucopenia occurs during the early stages of the disease, up to fifth or sixth day reaching its lowest point at the end of the first w of illness After this there may be a slight leucocytosis During the first days there is lymphopenia which gives place to granulopenia Later ther a relative increase of large mononuclears

A close study of hematologic changes is obviously a sine qua non in vestigating practically all diseases which can be designated "tropical or less."

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CHAPTER 69

HISTOLOGIC TECHNIC IN THE TROPICS

PHILIP HERMAN HARTZ

The pathologist who works in the Tropics will encounter certain difficulties such as high temperature high humidity and lack of trained personnel and of many conveniences which are easily available in more highly industrialized localities Such difficulties may be reduced to a certain extent by the choice of appropriate apparatus and methods These will certainly make the establishment of a laboratory more expensive but this expense will be more than compensated for by higher efficiency and better results

The problems of high temperature and humidity can of course be solved by air conditioning but few governments or other agencies setting up a laboratory for pathologic histology will be inclined to appropriate the funds for such installations

Since it is assumed that the reader has a certain familiarity with histopathologic technic only those points and methods will be mentioned which are considered of special interest for work in the Tropics

LABORATORY ROOMS

If possible the laboratory rooms should have windows facing north or northeast (if north of the equator) Since dust interferes with proper tissue work the windows must be made of glass and must be so constructed that only the upper third can be opened The floors must be stone or tile There should be many cabinets with well fitting doors which can be closed in order to keep out cockroaches and other insects For the storage of valuable material metal cabinets are used

FIXATION OF TISSUES

Good fixation is the primary and most important step in histopathology Since post mortem decomposition is very rapid in the Tropics autopsies should be made as soon after death as possible Prompt refrigeration of the bodies is very advantageous For special cases a metal stomach tube can be inserted through the esophagus into the stomach immediately after death and the stomach and eventually the duodenum filled with a fixing fluid (Hartz et al 1938) Surgical specimens should be fixed as soon as they are removed from the body If possible blocks no thicker than 3 mm should be cut to ensure rapid penetration of the fixative and to prevent autolysis in the center of the block Hollow organs such as stomach and gall bladder and cystic tumors should be opened prior to fixation when the thickness of the wall exceeds 3 to 4 mm thin blocks should be cut This can easily be done with surgical scalpels with detachable blades (Bard Parker etc) which still give very good service after having been used for surgery

On no account should specimens be left lying about for a time nor should large tumors or organs in their entirety or after a single incision be dropped into a fixative. Keeping tissues in physiologic saline will only *further autolysis*.

In surgical or gynecologic clinics a member of the staff should be made responsible for the proper fixation of the specimens, of course after being duly instructed by the pathologist.

Of almost equal importance is the choice of a proper fixative. Formalin for many pathologists the one and only fixing fluid cannot be considered as satisfactory. After fixation in formalin paraffin embedding causes marked shrinkage and the more delicate staining methods give on sections of formalin fixed tissues only mediocre or bad results (Masson 1923, Langeron 1934, Hartz 1945, Gomori 1947). Neither can Zenker's fluid be recommended since this fluid necessitates prolonged washing and moreover does not allow the cutting of frozen sections.

On the basis of an experience of many years we recommend Bouin's fluid as the best universal fixative especially for surgical material. It should be used in the modification of Masson (1923) or of Gomori (1947).

Masson's Modification of Bouin's Fluid

Water	30 parts
Formalin U S P	10 parts
0.5 to 2 per cent trichloracetic acid	2 parts
Picric acid in excess	

Gomori's Modification of Bouin's Fluid

Water	150 parts
Formalin U S P	50 parts
Glacial acetic acid	4 parts
Picric acid in excess	

The solutions can be used after one day during which time they must be shaken from time to time. In well stoppered bottles they keep indefinitely. Thin blocks of tissue are fixed in 18 to 24 hours; for very small specimens, for example liver punctates, 45 minutes are sufficient. Specimens should not *be left longer than 3 days in this fluid.* *After fixation in* Bouin's solution the consistency of the tissues is better suited for the frozen section technic than after formalin fixation and the microscopic details are better preserved (Hartz 1945). Paraffin embedding causes only little shrinkage and practically all staining methods give excellent results. When the preservation of the zymogen granules of the pancreas is important the mixture with trichloracetic acid should be used.

For fixation of kidneys, lymph nodes, spleen and bone marrow we prefer a mixture of equal parts of *Bouin's fluid and a saturated aqueous solution* of mercuric chloride (Hartz and Hugenholtz 1942). This mixture must be prepared immediately before use and should act for 12 to 24 hours.

Fixation in formalin is recommended only when the tissues cannot be embedded within a few days after fixation is completed, as is often the case

during scientific expeditions in tropical regions. In these circumstances the preservation of Bouin fixed material in alcohol or other fluids causes loss of its affinity for stains so that fixation in 10 per cent neutral buffered formaldehyde solution and storage in a 3 per cent neutral buffered solution of formaldehyde is to be preferred. It is a matter of course that for optimal results thin blocks must be cut. Thin blocks should be left at least 48 hours in the 10 per cent solution.

Neutral Buffered Formaldehyde Solution (pH 7.0)

(According to Lillie 1948)

37 to 40 per cent formaldehyde solution	100	c.c.
Water	900	c.c.
Acid sodium phosphate monohydrate	4	Gm
Anhydrous disodium phospate	6.5	Gm

When $NaH_2PO_4 \cdot H_2O$ and $Na_2HPO_4 \cdot 12H_2O$ are used, 4.02 and 16.37 Gm respectively are needed.

After fixation in Bouin's fluid, in the Bouin sublimate mixture and in formalin buffered to pH levels above 6.0 no formaldehyde precipitations are formed. This obviates the necessity of using alcohol as a fixative for the demonstration of malaria pigment.

Fixation must always be done in tightly closed jars to prevent evaporation.

FROZEN SECTION TECHNIC

(See Chapter 70)

It has already been stated that excellent frozen sections can be obtained from Bouin fixed material. When thin blocks are put in the fixing fluid and kept in the paraffin oven, frozen sections can be cut after one hour.

The freezing microtome should be equipped with a device for freezing the knife since this facilitates the cutting of soft material or of tissue containing much fat. Especially useful is the large blockholder of Ten Berge (1923) which fills with solid carbon dioxide and prevents the quick thawing of the blocks of tissue.

To remove the picric acid, sections of Bouin fixed material are treated for a few seconds with 50 per cent alcohol to which a few drops of a saturated aqueous solution of lithium carbonate have been added; they are afterward washed with water, stained on the slide with acidified Harris' hematoxylin, blued with tap water and mounted in glycerin gelatin. In this way a diagnosis can often be established in 10 to 15 minutes. After fixation the blocks must be embedded as soon as possible. They may be stored for a *few* days in 70 per cent alcohol.

EMBEDDING METHODS

For a pathologic laboratory the paraffin method is the most important. It allows the cutting of series of thin sections which can be stained by almost every method. Moreover, paraffin embedded tissues are easily stored and remain unchanged indefinitely.

In order to obtain good results with the paraffin method, careful dehydration is absolutely necessary. Insufficient dehydration causes marked shrinkage and distortion. Since it is often difficult to procure water free alcohol, fluid which removes not only the alcohol but also the last traces of water should be interposed between the alcohols and the paraffin solvent. For this purpose methyl benzoate containing one per cent of celloidin is highly recommended. The little delay caused by this method, originated by Peterfi (1921) is largely compensated for by the excellent results.

The best paraffin solvent is benzol, which must be free from thiophene. Instead of pure paraffin we use Tissuemat (Fisher Scientific Company, Pittsburgh, Pa.) with a 56° to 58° C melting point. When this is not available pure paraffin with a melting point of 56° to 58° C, mixed with 5 per cent yellow beeswax, is recommended.

Tissues fixed in Bouin or in the Bouin sublimate mixture are sufficiently hardened so that the use of graded alcohols in dehydration is superfluous.

The following sequence is proposed:

1 Alcohol, absolute (this alcohol may have been used once prior to this)	8 to 12 hours
2 Alcohol, absolute	8 to 12 hours
3 Alcohol, absolute	8 to 12 hours
4 Methyl benzoate containing 1 per cent celloidin 3 to 5 changes	24 to 60 hours
5 Benzene, 3 changes	30 to 60 minutes
6 Tissuemat, 3 baths	24 to 30 hours

The various time periods can be changed according to the size and number of the blocks. Hardened tissues can be left 5 days in the methyl benzoate. Masson (1923b) recommends the use of 3 paraffin ovens, one for every bath, so that the last oven is entirely free from benzol vapors. Good results can also be obtained with 2 ovens. The solution of celloidin in methyl benzoate is prepared by dropping *dry* shreds of celloidin or Parlodion in methyl benzoate and heating this to 80° C, or by leaving it in the paraffin oven. The bottle should be turned over from time to time.

*For special purposes the celloidin content of the methyl benzoate can be increased to 4 per cent so that a double embedding ensues. In this case the blocks are put through 2 baths of 1 per cent methyl benzoate, 1 bath of 3 per cent methyl benzoate, and 1 bath of 4 per cent methyl benzoate. They are then hardened in chloroform, which must be free from water, and embedded in paraffin after 2 baths in benzene.

MICROTOMES

For cutting paraffin sections the rotary type microtome (Minot) is the most practical. A very heavy and rigidly constructed model should be chosen as this permits cutting sections of equal thickness of hard material, which is often necessary in pathologic histology. The large rotary Leitz microtome is well suited for this purpose.

MICROTOME KNIVES

A well sharpened knife is necessary for cutting good sections. Until a short time ago the sharpening of microtome knives was a difficult and time consuming process. This has been radically changed by the introduction of the Aloe electric knife sharpener which reduces the time needed for honing a knife to 15 minutes and is invaluable for every pathologist who has to work with restricted personnel.*

Microtome knives should be carefully cleaned after use and coated with acid free oil to prevent rusting.

CUTTING OF PARAFFIN SECTIONS

In hot climates it is always advantageous to cool the paraffin blocks just before sectioning. This can be effected by various devices using carbon dioxide, but since this gas is often difficult to obtain and must be kept for the freezing microtome, the cheapest and simplest method consists in cooling the block already fastened on the microtome using an ice cube wrapped in filter paper and pressed against the block for a short time, after which a ribbon of sections can be cut.

When the sections have been cut, the exposed tissue should be dipped in melted paraffin, otherwise insects might destroy it in a short time.

ATTACHING PARAFFIN SECTIONS TO SLIDES

A small drop of albumin glycerin is smeared on the slide and heated gently over a small flame until a whitish vapor appears. After cooling the slides are covered with distilled water and the sections flattened on a Ranson embedding table. The sections are dried in a drying oven at a temperature of 45° C. Noncorrosive microslides and cover glasses should be used exclusively.

STAINING METHODS

For the Tropics, staining methods should be used which give constant results and which are not too complicated. The staining solutions must never be prepared in too large quantities. Precautions must be taken against rapid evaporation. Therefore the solutions must be kept in bottles with ground in stoppers, and for the staining of paraffin sections attached to slides Koplin jars should be used which can be fairly well sealed with petroleum jelly. To prevent the growth of molds, thymol must be added to many staining solutions, especially to those containing eosin, azophloxin and Ponceau.

Sections fixed in fluids containing picric acid are decolorized by 70 per cent or 80 per cent alcohol to which a few drops of a saturated aqueous solution of lithium carbonate have been added.

*The editor (R.B.H.G.) can recommend the Micro Sharp Company, Niagara Falls, N. Y., P. O. Box 363, for their excellent and unusual knife sharpening.

Hematoxylin

After many trials Harris alum hematoxylin has proved to be the most *stable*.

The method of making Harris hematoxylin is given on page 1513.

Counterstain

As a counterstain after hematoxylin eosin is still used in many laboratories. We have replaced it for many years by azophloxin (Gurr) which is more stable and gives very pleasant tones. It shows almost no fading even on *exposure to very strong light*. *A 0.2 per cent solution* is prepared from a 1 per cent stock solution and acidified by adding a few drops of 2 per cent acetic acid. Thymol must be added to both solutions to prevent the growth of molds. After staining the sections are transferred directly to 80 per cent alcohol, *not* to water.

Connective Tissue Stains

Two methods of staining connective tissue are routinely used in our laboratory. *The first is Larson's and Levin's (1940) modification of Masson's* trichrome stain which gives unusually clear details in neoplastic growths, especially in myomas.

Larson and Levin Modification of Masson's Trichrome Stain (1940)

Reagents.—

Hansen Trioxyhematein.—

Solution A. Dissolve 10 Gm. ammonium ferric alum and 1.4 Gm. ammonium sulfate in 150 c.c. of distilled water with heat.

Solution B. Dissolve 1.6 Gm. of hematoxylin in 75 c.c. of distilled water with heat.

Cool the 2 solutions, then pour solution A into solution B (never vice versa!), stirring constantly. When the mixture turns violet, heat it over the flame and test on filter paper *for a sepia or brownish black color*. *Remove the solution from the flame* immediately and cool by immersing the beaker in cold water. If the stain shows an olive green color on the filter paper it has been overoxidized. Do not boil the stain longer than 1 minute.

To 8 parts of the stain
add 2 parts of 1 per cent sulfuric acid.
Keep the rest as stock solution.

Ponceau Fuchsin Stain.—

Stock Solution

Crystalline Ponceau R (Gurr) *or* Ponceau xylidine (Krall)	1.5 Gm.
Acid fuchsin	0.5 Gm.
1% acetic acid	200 c.c.

Staining Solution

Stock solution	10 c.c.
0.5% aqueous azophloxin solution	2 c.c.
1% acetic acid solution	88 c.c.

Fast Green Solution.—

Stock Solution

Fast green F.C.F.	0.2 Gm.
1% acetic acid	100 c.c.

Staining Solution

Stock solution	15 c c
1% acetic acid	40 c c

Add the stock solution to the acetic acid

Technic —

Stain in Hansen trioxyhematein	2 to 5 minutes
Wash several minutes in tap water	
1% acetic acid	1 minute
Ponceau acid fuchsin azophloxin stain	5 minutes
1% acetic acid	2 minutes
2% phosphotungstic acid	1 minute
1% acetic acid	2 minutes
Fast green solution	5 minutes
1% acetic acid	3 minutes
96% alcohol 2 changes	
Clear and mount	

Lendrum Celestin Blue Hemalum Stain (1947)

The Hansen trioxyhematein stain can be replaced by the Lendrum stain

Stains —

Celestin Blue Lendrum.—

Allow 2 5 Gm iron alum to dissolve at room temperature
in 50 c c distilled water
Add 0 25 Gm of celestin blue (C T 900)
Boil for 3 minutes
Filter into a staining jar when cool
Add 7 c c glycerin

Mayer Hemalum —

Dissolve 1 Gm hematoxylin
0 2 Gm sodium iodate
50 0 Gm powdered potassium alum at room temperature
in 1 liter distilled water
Add 50 Gm chloral hydrate
and 1 Gm citric acid
Boil for 5 minutes
When cool it is ready for use

Technic —

Stain in celestin blue	5 minutes or less if fresh
Rinse in tap water	
Filter Mayer hemalum onto the tissue	5 minutes
Place in tap water until blue	
1% acetic acid	1 minute
Ponceau acid fuchsin azophloxin etc as given in the first method above	

Collagen

For deeper staining of collagen and of part of the reticulum and especially for the staining of sections of kidneys the Mallory Heidenhain or Azan stain is recommended This method gives beautiful results and the procedure can be shortened to little more than 1 hour

Stains —

Azocarmine —

Azocarmine G (Certified) ---------- 100 mg
Distilled water ---------- 100 c c

Add the azocarmine to the distilled water, and bring to a boil Cool to room te ture and filter

When cool, add 1 c c of glacial acetic acid

Aniline Blue —

Aniline blue (Certified) ---------- 0 5 Gm
Orange G (Certified) ---------- 2 0 Gm
Glacial acetic acid ---------- 8 0 c c
Distilled water ---------- 100 0 c c

Boil and filter after cooling

Technic —

Heat the azocarmine solution to 56° C

Stain sections in azocarmine for 15 minutes in the paraffin oven

Wash in distilled water

Differentiate in a mixture of 3 parts of 5 per cent aqueous phosphotungstic aci 2 parts of pure methanol The differentiation is complete in a few minutes (Ru

Wash in distilled water

Stain in aniline blue solution diluted 1 2 with distilled water, 30 to 50 minut

Wash quickly in distilled water

Differentiate in 95 per cent, followed by absolute alcohol

Clear and mount

Results Collagen and reticulum, deep blue; chromatin, red; muscle, red to or erythrocytes, red, mucin, blue

Fluoran-Thiazin Stains

Of this group the simplest and easiest is the following variant of Mann-Dominici stain·

Orange Eosin Mixture —

Eosin Y (Certified) ---------- 0 5 Gm
Orange G (Certified) ---------- 0 6 Gm
Distilled water ---------- 100 0 c c

Technic —

Stain with Harris hematoxylin and differentiate with HCl alcohol until only chromatin is stained

Wash several minutes in tap water

Stain in the orange eosin mixture for 20 to 30 minutes

Wash in distilled water

Stain in 0 5% toluidin blue 1 to 2 minutes

Wash in distilled water

Differentiate in 95% alcohol to which a few drops of 10% solution of colopho resin in absolute alcohol have been added Keep the slide in constant motion

Dehydrate in acetone

Place through 2 changes of xylol

Mount in Clarite

Nuclei, the cytoplasm of lymphocytes and plasma cells, and bacteria are blue, lagen and other tissue elements are pale rose color

MOUNTING OF SECTIONS

Before mounting in resinous media such as Canada balsam or Clarite, the sections must be dehydrated and cleared Since the alcohol used for dehydration may contain water, we always interpose 2 or 3 baths of pure water free terpineol (Gurr) between the alcohol and the paraffin baths Since terpineol is neutral, it is superior to the carbol xylol still used in many laboratories After Dominici's stain dehydration in acetone which in contrast to alcohol does not extract thiazin dyes is to be preferred As mounting media one of the synthetic resins should be used

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CHAPTER 70

RAPID FROZEN SECTION METHODS IN TROPICAL DISEASES

ARAM A KRAJIAN

INTRODUCTION

Rapid and accurate examination of tissue is one of the most important procedures in a modern hospital laboratory both in temperate and in tropical countries It is essential to eliminate from laboratory methods as completely as possible all lost time and lost motion without in any way affecting the accuracy of the procedures The specialty is already so overcrowded with methods that any saving of time especially with promise of increased exactitude should be welcomed by the clinical pathologist and laboratory worker (See Chapter 69)

Three methods are commonly used for preparing microscopic sections the paraffin the celloidin and the frozen methods

The celloidin method is very seldom used routinely and in only a few places The most common and most popular procedure has been the paraffin method The frozen section method is used in some laboratories as a routine practice and in others only as an emergency measure

Frozen sections when properly made are superior to *paraffin sections* *In* the paraffin embedding process it is impossible to prevent shrinkage of the tissue

The advantages of the frozen section method are (1) ease of manipulation (2) economy (3) no change in the normal structure of tissue and (4) rapidity

THE FROZEN SECTION METHOD

(Krajian 1940)

There are certain salient features which must be determined and followed in order to secure correctly made frozen sections

The Formaldehyde Solution and How It Is Used

Ten per cent formalin solution is made by diluting 10 c c of commercial 40 per cent formaldehyde solution (formalin) to 100 c c with tap water Immediate fixation is essential Tissues should be placed in formaldehyde solution as soon as possible after removal from the body At least 15 times as much fluid as bulk of tissue must be used The pieces of tissue should not be too thick Tissues should be immersed in a 15 per cent neutral formalin solution for the first 24 hours (15 c c of formalin diluted to *100 c c with tap* water)

For rapid fixation as for example biopsy examination at the operating table the formaldehyde solution must be boiled A very thin block of biopsy material is cut and then dropped into the boiling formaldehyde solution This is shaken constantly for 30 seconds For rapid fixation of autopsy material the formaldehyde solution is brought to the boiling point in a test tube This solution is poured over the tissue in a bottle reducing the temperature of the formaldehyde solution to about 65° C The tissue is then placed in an oven regulated at 56° C for 20 to 30 minutes and the routine procedure for frozen sections carried out With this method shrinkage will be no more than 5 per cent whereas routine paraffin sectioning methods cause shrinkage varying from 15 to 30 per cent

After 24 hours fixation tissues should be cut into blocks about 1 or 2 cm square and from 3 to 5 mm thick and placed in 10 per cent neutral formalin

Neutrality of formalin is very important in preserving the staining qualities of the nuclei For neutralization add 5 Gm of calcium carbonate or sodium bicarbonate to a gallon of stock formalin (40 per cent formaldehyde)

Cutting Frozen Sections

Washing the Block—Place the blocks in tap water in a 250 c c beaker to remove the formaldehyde which not only is harmful to the skin of the operator but also prevents the block from adhering to the object holder This immersion in water should be for a short period of time only

The Microtome and Blade—The knife should be honed and stropped so that the edge has a shorter bevel on one side than on the other it should be used with the shorter bevel downward The block holder should have deep grooves The Bausch and Lomb freezing microtome (newer type) is recommended Place a drop of water on the holder then put the block of tissue on the holder An angle of the block rather than a straight edge should face the knife If the tisue is covered with a capsule such as skin or mucous membrane this capsule surface must face the knife edge at an angle and should never be placed on the side away from the knife

How to Freeze the Block—Place the index finger on the block to hold the tissue in place then turn on the CO_2 gas slightly for temporary holding Press down firmly all around the tissue to fix it to the holder then release more gas slowly until the freezing level has passed upward through about one *half of the entire block If any part of the section is not frozen holes will* occur in the tissue since the unfrozen portion will break

Cutting the Section—Cut off the upper third of the tissue that is the unfrozen portion and drop it back into the specimen bottle Then shave down to establish a smooth level surface If the surface to be cut is frozen too firmly it is hard and white and the sections will be fragmented If the surface is too soft the sections will have holes The ideal is a hard pliable surface so that a section cut therefrom will show no tendency to break as it piles up over the cutting edge of the knife

How to Operate the Microtome—Do not use a microtome where the constant rotation of the wheel lifts the block holder This faulty method largely due to the manufacturer s wrong idea of making things look easy is responsible for poor frozen sections The automatic lifting attachment on the microtome must be removed and each section cut slowly Place the hand on the rim of the flywheel and turn it slowly Rapid use of the wheel as is ordinarily *carried out in many laboratories* does not allow sufficient time to adjust the tissue surface to the proper temperature and consistency The method we recommend slow turning by hand permits warming of the cut surface of the block giving a pliable section free from undulations

Turn the notched micrometer wheel with the left hand then operate the flywheel with the right hand *Use three notches which will enable one to cut* a section about 10 microns thick Uneven sections are usually the result of freezing the block too hard applying too fast a speed and unnecessary force especially on firmer tissues

How to Remove the Section From the Knife—Wet the tip of the little or ring finger with water carefully remove the section from the edge of the knife and place it in water Then dry the knife edge and keep it dry Water left on the edge thaws the tissue with which it comes in contact causing holes in succeeding sections Cut one section at a time remove it from the knife and place it in water Place the sections in a large dish of water over a dark background

How to Transfer Sections to Glass Slide—Clean the glass slide in 0 5 per cent acid alcohol and wipe dry The vessel in which the sections are floated should be at least 7 cm deep and 15 cm in diameter The operator should be seated so as to prevent any direct reflection of light from the slides to the eyes A glass rod pointed or slightly bent should be used to transfer the sections *of delicate internal organs to the slide* *Teasing needles may* be used for sections of firm tissues but not when staining for iron or using silver solutions

Anchor the section to the slide at about a 45 degree angle with three fourths of it under water in such a way that the edge of the water basin will afford support to either the slide or the fingers and thereby aid in steadying the slide Put the section by means of a glass rod on the middle of the slide bringing it to the surface of the water immediately above the center of the slide Now manipulate the slide with only part of the tissue under water in such manner as to straighten out most of the folds in the section The part of the tissue still in the water floats out on the surface of the water and by successively turning the slide the folds can be eliminated without touching the rod *or needle to the tissue* *After* the folds have been removed tilt the slide against a staining dish face down at a 45 degree angle so that the excess water may partially drain off Do not permit the section to dry Fifteen seconds to 1 minute is usually sufficient depending on the atmospheric conditions of the room

Dehydration of the Section

Drop at short range to prevent breaking the section hydrous isopropanol or absolute ethyl alcohol on the sectio at a slight angle to the dropping bottle Blow the brea until the alcohol seems to have evaporated Then blot it eral thicknesses of fine filter paper Next flood with isop alcohol for complete dehydration 1 to 10 minutes Pour ing careful not to disturb the section In fatty tissues fat alcohol and the section may tend to slip from the slide I stances blow over the surface of the section gently and rer alcohol by evaporation to keep the section on the slide Bl paper then dip twice rapidly into a jar containing thin cell over the surface blot twice and place immediately in th Note that we advocate the use of celloidin rather than May and regard the celloidin method as far superior Celloid Du Pont Schering or Mallinckrodt Prepare a solution of sistency of a thick syrup To prepare a thin celloidin solu to attach sections to the slides mix 1 part of the thick cell of a mixture of equal parts of absolute ethyl alcohol and et of a saturated alcoholic solution of gum mastic is added

Routine Staining of Frozen Sections

Harris Hematoxylin—For routine nuclear staining Harris hema rather than other types of hematoxylin solution It is [illegible]

Hematoxylin crystals
Absolute alcohol
Ammonium or potassium alum
Distilled water

Dissolve the hematoxylin in the alcohol Dissolve the alum in and add the hematoxylin solution Bring the mixture to a boil then add 0 5 Gm mercuric oxide The solution at once assumes a dar this occurs remove the vessel containing the solution from the flam as possible in running water or in frequently changed cold water I cool Add 3 cc of glacial acetic acid to [illegible] cc of the solution just the nuclear staining properties

Acid Alcohol.—Add 1 cc of concentrated hydrochloric acid to 1 alcohol

Ammonium Isopropanol—Add 5 cc of ammonium hydroxide to isopropanol and mix If the ammonia volatilizes off add more ammo

Carbol Xylol—One part liquefied carbolic acid and 3 parts of xyl

Gum Damar—Dissolve gum damar in xylol until the desired co then allow to settle and decant the clear supernatant portion

Eosinol (Krajian 1938)—Simplicity and dependabil hematoxylin eosin its place as the standard routine tissue st able because it tolerates wide variations in material and

eosin stains the tissue comparatively slowly and then is partially extracted by the dehydrating alcohols The margin of safety between excessive extraction of eosin and complete elimination of the water is not always sufficient to insure good results

A change in the manner of applying eosin is described here This not only corrects this difficulty but also offers the advantages of a more powerful stain, with economy of alcohol and saving of time

The principle of the modification consists in the dehydration of the section before counterstaining and the application of eosin as a solution in carbol xylol Then since the tissue passes thereafter through xylol only, there is no opportunity for decolorization Alcohol is saved because dehydration can be commenced in the stronger alcohol, which obviates the use of the lower gradations The solution of eosin in carbol xylol, which constitutes the principal element of modification, may be called for convenience "eosinol"

Dissolve 5 Gm of aqueous eosin in 10 c c of distilled water

Precipitate it by adding 10 c c of glacial acetic acid, and 2 c c concentrated hydrochloric acid, and mix with a glass rod

Incubate the resulting coagulum at 56° C for 12 to 16 hours or until all the water has been evaporated

Dissolve this dehydrated acid eosin in a mixture of 10 c c of absolute alcohol and 20 c c of acetone, stirring with a glass rod for several minutes

Let the undissolved portion, which is to be discarded, settle to the bottom of the container This requires about 10 minutes

Remove the clear portion with a clean, dry pipette or medicine dropper

Add it to 1,500 c c of carbol xylol, made by mixing 1 part of pure melted phenol crystals with 3 parts of neutral xylol Some precipitate will form, which will settle to the bottom of the container The clear portion is the eosinol This solution keeps indefinitely

Owing to variation in the staining power of the various brands of powdered eosin it may be necessary to standardize the solution by staining control sections and adjusting the strength of the eosinol by reducing or increasing the amount of carbol xylol

Technic of Staining —

Place frozen sections in Harris hematoxylin for 3 to 5 minutes

Rinse and place in tap water until blue, 1 to 2 minutes

Destain in acid alcohol, dipping in and out for even destaining, and stopping when no more color leaves the section

Place in tap water for a few seconds to a few minutes

Place in the ammonium isopropanol mixture until the section is blue

Pour 2 or 3 drops of anhydrous isopropanol over the slide

Repeat this process twice for complete dehydration

Dip in eosinol several times until the background is stained evenly red, which requires 10 to 30 seconds depending upon the strength of the solution

Place in carbol xylol for 3 minutes

Transfer to first xylol for 2 minutes

Transfer to second xylol for 2 minutes

Transfer to third xylol for 2 minutes

Mount in neutral gum damar

In all cases where sections are transferred from one solution to another, be sure to drain off as much of the solution as possible, especially the carbol xylol Carrying of carbolic acid into xylol dishes will cause fading of the nuclear stain

If the sections occasionally fall off, due to swelling, flood them with isopropanol for 2 to 3 minutes pour off the isopropanol, blow over the section until it is dry, blot, and dip twice in celloidin Resume the staining process from that point

Serumizing Method for Loose Textured Tissues

(Krajian 1939)

One of the principal objections to the preparation of routine permanent sections by the freezing method has been the difficulty in keeping intact the loose textured or necrotic tissues such as abscessed lungs, degenerated tumor masses, congested spleen, kidney glomeruli, endometrial tissue, testicle, thymus, etc. We have overcome this defect by developing an effective method of infiltrating such tissues with blood serum and then coagulating with dioxane. This permits the preparation of complete frozen sections from biopsy and autopsy material, thus avoiding the delay and unnecessary extra expense of preparing routine paraffin sections.



Fig 463 —Photomicrograph showing coccidioides in biopsy section of skin, hematoxylin and eosin stain

The Method.— Serumizing. —Fix the loose textured tissues in 10 per cent formalin in the usual manner for 24 hours or longer.

Then trim the blocks and wash them several times in tap water to remove the formaldehyde.

Place the blocks in a small Stender dish or specimen bottle containing uncontaminated human or animal serum. Fresh serum from serologic tests is an ideal medium. The amount of serum should be ample to cover the tissues.

Cover the dish or bottle tightly and place in a warm place overnight. The top of the paraffin oven is a good place for it. Any floating tissue such as lung or fatty material should be covered with absorbent cotton in order to keep all parts in the serum.

Decant the excess serum after overnight infiltration and without washing add dioxane to cover the blocks. Let stand for 3 to 5 hours or until complete coagulation occurs.

Without further fixation *freeze the blocks on a freezing microtome using CO_2 gas* and cut, stain and mount as usual.

The blocks cannot be kept in dioxane indefinitely as it causes slow shrinkage of the tissue. After cutting the sections place the blocks in 10 per cent formalin to keep them permanently.

For emergency examination, place very thin blocks of formalin fixed tissue in serum in a paraffin oven at 56° C for 2 hours, coagulate in dioxane for 2 hours, then cut and stain

This method causes very little shrinkage, but no curling or shriveling of sections as in other embedding processes devised for frozen sections, such a gelatin embedding The infiltrating serum, when it is completely coagulated by the action of the dioxane, acts as a supporting medium to furnish stability and to hold cells and intracellular structures in proper relation to each other it does not interfere with any staining process as does the gelatin method

Serumizing hard tissues, such as bone and uterus makes them soft and pliable and produces better sections

Fresh serum may be stored in small bottles and preserved by adding ' c c of *40* per cent formaldehyde (formalin) to each *50* c c of serum This serum can be kept at room temperature for several months without becoming contaminated

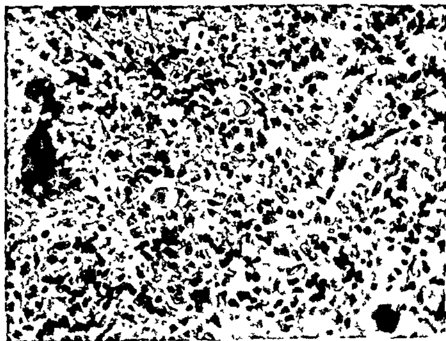


Fig 414 —Photomicrograph showing blastomyces in a section of biopsy of the skin (hematoxylin and eosin stain)

Frozen Sections at the Operating Table

This method which is both rapid and permanent has proved singularly efficient

Trim a thin block of biopsy tissue and drop it into a Pyrex test tube containing boiling 10 per cent formalin Shake vigorously for one half minute

Wash rapidly in tap water, then freeze rapidly with CO

Cut sections and transfer to a glass slide

Apply 3 or 4 drops of anhydrous isopropanol or absolute ethyl alcohol to the section and blow gently over the surface until the alcohol is completely evaporated then blot with several thicknesses of fine filter paper and dip once in thin celloidin

Blow over the section until dry, blot, and stain in Harris hematoxylin, dipping in and out about 40 times

Wash rapidly in tap water and destain in acid alcohol by dipping the slide in and out turning the slide each time

Neutralize and dehydrate in ammonium isopropanol mixture (see above) until blue

Dehydrate completely in 2 changes of isopropanol

Dip in and out of eosinol for a few seconds until the background is red.

Dip in and out of carbol xylol about 20 times

Dip in and out of xylol about 20 times

Mount in gum damar

For celloidin and paraffin methods see Chapter 69 and Gradwohl (1948)

SPECIAL METHODS OF STAINING

The Clinical Application of a Rapid Staining Method for Treponemata in Tissue Sections

The biopsy method for the demonstration of spirochetes is the most satisfactory and dependable method of examination for Treponemata the efficiency is 100 per cent from the first day of the appearance of the lesion up to 3 months or more, in syphilis A 20 minute staining method of examining biopsy material for spirochetes was developed by Krajian (1939)

The Twenty Minute Staining Method for Treponemata in Frozen Tissue Sections (Krajian, 1939)*

Reagents —

Primary Solution.—

Uranium nitrate	1 Gm
Formic acid, 85 per cent	3 c c
Glycerin	5 c c
Acetone	10 c c
95 per cent alcohol	10 c c

This solution is stable and keeps indefinitely

Saturated Alcoholic Solution of Gum Mastic —Dissolve 25 Gm of gum mastic in 35 c c of absolute alcohol Shake the solution several times a day for several days until solution is complete Allow to stand until clear This solution can be centrifuged for rapid clarification Use only the clear portion The dilute solution is prepared from this stock solution as needed

Ten Per Cent Silver Nitrate Solution.—Dissolve 10 Gm silver nitrate c p, in distilled water and dilute to 100 c c with distilled water Keep in a well stoppered bottle at room temperature This solution keeps well

One Per Cent Silver Nitrate Solution.—This solution is made just before use by diluting 3 c c of the 10 per cent solution to 30 c c with distilled water

Developing Solution.—

Hydroquinone	0 31 Gm.
Sodium sulfite	0 1 Gm
Acetone	2 5 c.c.
40 per cent formaldehyde	2 5 c c
Pyridine	2 5 c c
Gum mastic, saturated alcoholic	2 5 c c
Distilled water	15 0 c c

*The paraffin method is discussed in Gradwohl (1948)

Completely dissolve the hydroquinone and sodium sulfite in the formalin acetone solution Then add the pyridine and gum mastic Mix well Finally add the water and invert for thorough mixing

This solution keeps well for about 2 weeks in the light, after which it deteriorates, the gum mastic separating and settling to the bottom of the container If this occurs, a fresh supply should be prepared

The developing solution must be warmed to 60° C for 15 minutes before use

The Method.—

Boil 10 per cent formalin in a Pyrex test tube, drop a small piece of biopsy material into it, and agitate for 1 minute Regular formalin fixed tissues do not require this treatment

Cut frozen sections 7 to 10 microns thick

Place the sections in the primary solution, previously heated to 60 ° C, for 5 minutes, keeping the dish in a paraffin oven or water bath at 56° to 60° C

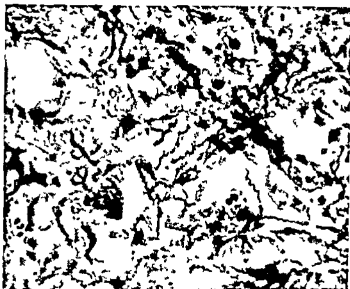


Fig 465 —Photomicrograph showing *Treponema pallidum* in liver section from a case of congenital syphilis (Krajian 20 minute stain)

Rinse in distilled water

Treat for 5 seconds in dilute gum mastic solution made by mixing 3 drops of saturated alcoholic solution of gum mastic in 5 c c of 95 per cent alcohol

Rinse and spread out sections in distilled water

Place sections in a wide mouth Pyrex beaker or other suitable Pyrex receptacle containing 30 c c. of freshly made 1 per cent silver nitrate solution Place the beaker containing the sections over a flame about 4 feet below a 60 watt electric light

Heat the silver solution until bubbles form Place a thermometer in the beaker and maintain a temperature of 67° to 70° C for 7 minutes

Without washing, carry individual sections with a glass rod lifter to the warm developing solution, alternately dipping the section into the solution and then exposing all portions of it, on the lifter, to the 60 watt light Repeat this process several times or until the section turns brown

Wash for a few seconds in 95 per cent alcohol

Without washing, again place the section in 1 per cent silver nitrate solution for 20 to 30 seconds

Rinse in distilled water

Place the sections in a large basin of distilled water and then transfer to a glass slide Since the section is brown there should be a white background under the basin

Blot with fine filter paper

Dehydrate for 30 seconds with absolute alcohol or anhydrous isopropanol

Blot twice with filter paper and dip in thin celloidin once Wipe the back of the slide with a clean towel

Treat with creosote xylol for 2 minutes (1 part creosote plus 2 parts of xylol)

Clear in pure xylol for 2 minutes

Mount in gum damar, placing an identification number or the patient s name under the cover slip for a permanent record



Fig. 466—Photomicrograph of *Leptospira icterohaemorrhagiae* in smear preparation from a culture of an acute case of Weil s disease (Krajian 20 minute spirochete stain.)

A Rapid Staining Method for Gram Positive and Gram Negative Organisms in Frozen and Paraffin Sections (Krajian)

In this method, the solutions used are methylene blue as a gram positive stain, fuchsin creosote as a gram negative stain and creosote xylol as a differentiator

1 The Frozen Section Method

Reagents —

Loeffler s Methylene Blue —

Saturated alcoholic solution of methylene blue	30 c c.
1 10 000 potassium hydroxide	100 c c

Creosote Xylol.—Mix 1 part of creosote with 3 parts of xylol

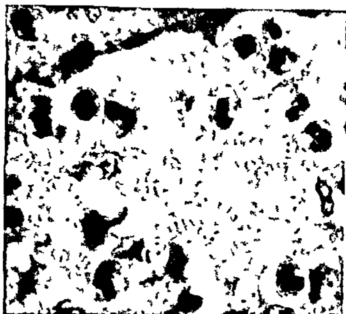


Fig 467—Photomicrograph sho ving *Klebsielia pneumon ae* (encapsulated) from a case of Friedländer pneumonia, stained by Krajian bacterial stain

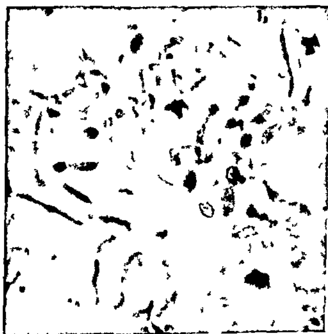


Fig 468—Photomicrograph sho ving *Mo il a albicans* in kidney section (Krajian bacterial sta n)

Creosote Fuchsin.—

Creosote xylol	50 c c
Six per cent alcoholic basic fuchsin	3 c c.

Technic—

Prepare mounted frozen sections 7 to 10 microns thick in the usual manner

Stain for 3 minutes with Loeffler's methylene blue

Wash in tap water and dehydrate rapidly with 3 applications of anhydrous iso propanol or absolute ethyl alcohol

Differentiate rapidly with creosote xylol agitating the slide constantly for 5 to 10 seconds

Pour off and apply creosote fuchsin agitating the slide about 20 to 25 times changing the solution once

Blot and apply creosote xylol 2 or 3 times agitating the slide constantly for even decolorization or until most of the excess red color leaves the section

Blot clear for 2 minutes in xylol and mount in gum damar

2 The Paraffin Section Method

Technic—

Deparaffinize the section with 2 applications of xylol and 2 applications of absolute alcohol or isopropanol

Hydrate gradually, in the usual manner and place the slides in tap water

Proceed as for frozen sections

With this method nuclei are red gram positive organisms blue gram negative organisms red devitalized gram positive organisms red yeast and molds blue, Negri bodies bright red with bluish chromatin bodies rickettsial and Donovan bodies red and fibrin sometimes blue and sometimes red

All staining solutions are stable

A Dependable Method for Demonstration of Acid Fast Organisms in Tissue Sections (Krajian)

Reagents—

Carbol Fuchsin.—

Hydrobromic Acid Alcohol—*Add 1 c c of hydrobromic acid to 100 c c of 60 per cent ethyl alcohol.*

Loeffler s Methylene Blue—

Iso Creosote Mixture—*Equal parts of anhydrous isopropanol or absolute alcohol and beechwood creosote*

Technic—

Cut frozen sections 7 to 10 microns thick

Transfer to a glass slide dehydrate blot in filter paper and dip in celloidin Blow over the surface until dry Wash in tap water until the surface is wet.

Place on a tripod or on a warming table apply carbol fuchsin and steam gently with a flame for 3 minutes

Discard the staining solution wash with tap water and apply hydrobromic acid alcohol with a medicine dropper 2 to 4 times agitating the slide constantly for even destaining or until most of the red stain is removed

Wash in tap water and apply Loeffler s methylene blue solution for 3 minutes

Wash in tap water and dehydrate with 3 applications of anhydrous isopropanol or absolute ethyl alcohol.

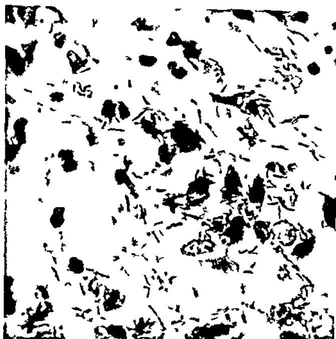


Fig 469—Photomicrograph sho ving *Mycobacter u l prae* in biopsy section of the arm in leprosy (Krajian acid fast stain)

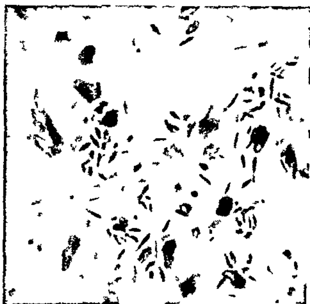


Fig 4 0—Pl oton crograpl sho ing Sporotricl um in section of testicle sta ned by I raj an bacterial sta n.

Immediately apply iso creosote, 2 or 3 applications, agitating the slide constantly for even differentiation This removes the excess blue from the tissue as well as from the organisms This is the "crucial" step, if it is overdifferentiated, the background will be very light blue without affecting the organisms light blue is the correct color

Blot immediately in filter paper

Clear in 3 changes of xylol 1 minute each

Mount in gum damar

For paraffin sections remove the paraffin with 2 applications of xylol 2 minutes each

Remove the xylol with 2 applications of anhydrous isopropanol or absolute ethyl alcohol

Wash in tap water and proceed as for frozen sections

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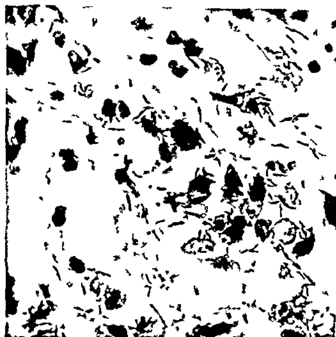


Fig 469 —Photomicrograph sho ing *Mycobacter un leprae* in biopsy section of the arm in leprosy (Krajian acid fast stain)

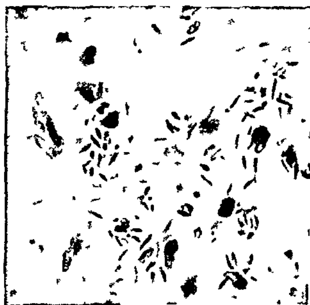


Fig 4 0 —Pl oton crograpl sho ing Sporotricl um in section of testicle stal ed by Kraj an bacter al stain

Immediately apply iso creosote, 2 or 3 applications, agitating the slide constantly for even differentiation This removes the excess blue from the tissue as well as from the organisms This is the "crucial" step, if it is overdifferentiated, the background will be very light blue without affecting the organisms, light blue is the correct color

Blot immediately in filter paper

Clear in 3 changes of xylol, 1 minute each

Mount in gum damar

For paraffin sections, remove the paraffin with 2 applications of xylol, 2 minutes each

Remove the xylol with 2 applications of anhydrous isopropanol or absolute ethyl alcohol

Wash in tap water and proceed as for frozen sections

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CHAPTER 71

COLLECTION, PRESERVATION, AND EXAMINATION OF STOOLS IN THE TROPICS

OSCAR FELSENFELD AND VIOLA MAE YOUNG

In addition to the usual difficulties encountered in the collection of stools one faces in the Tropics other obstacles such as the overgrowth of secondary organisms like Protei and greater instability of culture media due to the moisture and heat

Since this volume is not a laboratory manual but is devoted more particularly to the clinical side of tropical medicine only those steps are described which are useful in bedside or office examinations or those which can be performed with a minimum of equipment in a small laboratory

COLLECTION OF SPECIMENS

It is imperative that the stool be absolutely fresh This means that it must be examined within a few minutes after it has been collected If this basic rule of stool examination is not followed the amebae disintegrate and sensitive microorganisms either die or are so outgrown by secondary microorganisms that they cannot be easily recovered

The most suitable portion of stool for examination is mucus If no mucus is found samples are taken from the surface and from the inner portions of the specimen

When the patient is suspected of having or is known to have a disease in which the pathogenic organisms are situated in the higher portions of the intestinal tract and no diarrhea is present postcathartic stools must be examined Such specimens are helpful in the detection of carriers of Salmonellae Giardia and *Endamoeba histolytica* Postcathartic stools are collected after the patient has received 1 to 3 teaspoonsful of sodium or magnesium sulfate in one half glass of water before breakfast The samples for examination are collected from the second bowel movement after this catharsis

Manson Bahr (1943) suggested the examination of rectosigmoidoscopic samples for incitants of dysenteric disorders D Antoni (1942) described a method for detecting such organisms This consists of a cleansing enema about 1 to 1 5 hours before sigmoidoscopy Then an enema with about 2 liters of tepid saline is given The last part of the returned enema fluid is used for examination Finally aspiration samples are taken from the bowel walls through the sigmoidoscope When a cathartic is given before the enemas postcathartic stools may also be collected

Another method for rectal examination is the swab of Hardy and Watt (1942), which consists of a 10 to 12 cm piece of rubber tubing of 0 18 cm

outside diameter fitted over a regular throat swab The throat swab is prepared from a wooden applicator with one end covered by rolling cotton tightly over it Before use the end of the applicator is inserted just inside the rubber tube The end of the tube is lubricated and inserted for a distance of about 5 to 6 cm into the rectum Now the swab is exposed by withdrawing the tube 2 or 3 cm The swab is gently rotated, then withdrawn into the tube and the whole is withdrawn from the patient The tubing is discarded into a container and sterilized by boiling The swab is used immediately to streak plates and to make permanent stained slides for examination for intestinal protozoa Because of the lubricant the fecal material on the swab cannot be used for saline and iodine stained suspensions for direct examinations

Rectal biopsy is useful for the detection of intestinal schistosomiasis

PRESERVING FLUIDS

When a parasitologic examination cannot be carried out immediately the stool is mixed with about 10 times its volume of 10 per cent formalin Formol fixed material however is not very suitable for detailed protozoologic studies Schaudinn s method is preferred if it is possible to carry it out with the facilities available This fixative is also indispensable for the preparation of permanent hematoxylin stained slides Recently Schaudinn s fluid with the addition of polyvinyl alcohol (P V A) has been recommended (Page 1566)

For the latter purpose several slides preferably with frosted edges are prepared The name and number of the patient are written with graphite pencil on the frosted glass If the stool is hard some saline is dropped on the farther end of the slides For liquid stools a thin coat of egg albumin is used The sample is mixed with the saline or spread over the egg albumin with the aid of a wooden applicator The slides are immediately dropped into a modified Schaudinn solution

Modified Schaudinn Solution —

Saturated solution of bichloride of mercury in distilled water	200 c c
95 per cent ethyl alcohol	100 c c

Before use add to each 100 c c of th s mixture 7 c c of glacial acetic acid While the mixture of subl mate and alcohol keeps indefin tely the fluid after the addit on of acetic acid must be renewed each week

The fixative is kept in a Koplin jar The slides are put into it back to back When 2 slides are made from each stool specimen the material from as many as 5 stools can be fixed in 1 jar The slides remain in the fixative for at least 8 hours but not longer than 48 hours They may be mailed or sent by messenger to another laboratory for staining if this is not carried out locally

If a bacteriologic examination cannot be carried out immediately preserving fluids are used When only a few hours elapse between collection and examination of the material it is put into 1 per cent trypticase or tryptone broth Rectal swabs may be dropped into tubes containing such broth

When longer preservation is necessary, that is when the specimens are to be shipped buffered glycerine saline or desoxycholate citrate (Gradwohl 1948) is used

Add 1 or 2 Gm of stool, about 5 c c of urine, or 5 to 7 c c of blood to about 20 c c of the preservative

If suspicion of cholera exists, the preserving fluid of Wilson and Reilly (1940) is used

STOOL EXAMINATION

A For Protozoa

1 Direct Smears

Prepare at least 2 slides

On one end of 1 slide, place a drop of saline

On the other end, place a drop of D'Antoni's iodine (Chapter 73) (Gradwohl and Kouri 1948)

On the second slide, place 1 drop of D'Antoni's iodine at one end and at the other end a drop of 0 5 per cent methylene blue in saline

Emulsify small amounts of the stool in each drop

Cover each drop carefully with a separate cover slip in such manner that the drops remain separated

Inspect the saline suspension immediately

The other preparations must be examined after a few minutes (2 to 4), but before they dry

If the examination is carried out quickly a warm stage is not necessary

2 Zinc Flotation

The technic of Faust et al (1939) in the modification of Otto et al (1941) is used

Mix a portion of the fecal specimen, about the size of a bean with 33 1 per cent zinc sulfate, specific gravity 1 18 in a small vial 5 cm deep and 1 8 cm in diameter

Fill the vial with this solution until the meniscus is rounded over the edge of the tube

Place a cover slip on the surface and let stand 1 hour

Next place a drop of D'Antoni's iodine (Gradwohl and Kouri 1948) on a slide and put the cover slip on it in such a way that the slide which lies on the surface of the stool zinc sulfate emulsion rests on the drop of iodine

Examine under the microscope

Other methods of concentration are described in the chapters on parasitology

3 Permanent Hematoxylin Stained Slides

Any recommended procedure may be used We have had excellent results with a slightly modified method of Ratcliffe and Parkins (1944) (Felsenfeld and Young, 1945 Gradwohl, 1948) Slides fixed in Schaudinn's fluid are used for this staining

4 Diagnostic Culture

It seems that the results of diagnostic cultivation of protozoa are less favorable than those achieved with other methods

B For Helminths

See Chapter 72

C For Bacteria

Shigellae and Salmonellae (Including S Typhosa)

The methods used for this purpose depend on whether the laboratory prepares its own media or buys the desiccated products

a Laboratories Which Prepare Their Own Media —

Each stool specimen must be inoculated into

(1) One tube of Kauffmann's medium (Gradwohl 1948a)
(2) Streak one plate of Hajna and Perry (Gradwohl 1948b)
(3) Streak two D E C plates of Panja and Ghosh (1943)

D E C Plate —The D E C plate is excellent for the isolation of all types of Salmonella and Shigella Cholera vibrios grow well on it It is prepared as follows

Dissolve	Meat extract	5 Gm
	Peptone	5 Gm
	Sodium taurocholate	8 5 Gm
	Agar	25 Gm
in	Distilled water	1000 c c

Sterilize for 20 minutes at 15 pounds pressure
For use melt and adjust the reaction to pH 7 0 to 7 2

Add	Dibasic sodium phosphate	7 5 Gm
	Sodium citrate crystals	8 0 Gm
	Sodium thiosulfate crystals	8 5 Gm
	Lactose	12 5 Gm
	Ferric citrate scales	3 0 Gm

Adjust the reaction to pH 7 4 and add 15 c c of a 0 25% watery solution of neutral red certified

Boil for 2 minutes then pour in plates

The second day streak the growth from Kauffmann's tube to 1 plate of Hajna and Perry medium and 1 plate of Panja and Ghosh medium

Incubate all plates for 24 hours Incubate the Hajna and Perry plates for 48 hours

Pick up suspicious colonies and transplant to either Hajna's (1945) medium or to the commercial triple sugar iron agar

Organisms which produce an alkaline slant must be further tested as follows

(1) *Alkaline slant acid butt no hydrogen sulfide* May be a Shigella or a slow hydrogen sulfide forming anaerogenic Salmonella (e g typhoid bacillus)

Inoculate the growth into peptone or tryptone broth Test the original culture on the surface of Hajna's or triple sugar iron medium with Shigella antisera (Gradwohl 1948c) and typhoid "O" (Salmonella IX XII) serum

If further differentiation by chemical reactions is needed, inoculate the growth from the peptone or tryptone broth into further media

(2) *Alkaline slant, acid butt, some hydrogen sulfide* Test for *Salmonella typhosa* (exceptionally, *Shigella alkalescens*)

(3) *Alkaline slant, acid and gas in butt, hydrogen sulfide formed or not* It may be a Salmonella, Paracolon or Proteus The preliminary tests must include motility, mannitol fermentation, fermentation of sucrose, lactose, and salicin, indol and Voges Proskauer tests Salmonellae are usually motile, ferment mannitol, do not attack sucrose, lactose, or salicin, do not form indole, and do not give a positive Voges Proskauer reaction

b **Laboratories Which Buy Prefabricated Media —**

The following media are inoculated with stools

(1) One tube of tetrathionate broth, Difco, or Selenite F, Baltimore Biological Laboratory

(2) Streak 2 S S Difco plates *or* 1 D C and 1 D C L S plate Baltimore Biological Laboratory

(3) Streak 1 bismuth sulfite plate, Difco

The growth in the tetrathionate broth is streaked, the second day, onto 1 D C and 1 bismuth sulfite plate

The procedure is then as described above

c **Examination of Organisms Suspected of Being Cholera Vibrio —**

(1) Pick suspicious colonies from the D E C plate of Panja and Ghosh (above) and transfer to tryptone or medopeptone broth

(2) After 6 to 8 hours' incubation, make Gram stain and observe the morphology of the organisms

(3) Make slide agglutination tests if possible with Inaba and Ogawa sera

(4) Inoculate one tube of each lactose broth, sucrose broth, arabinose broth, and tryptone broth

Keep the original tryptone broth culture for the indol test

The "true" cholera vibrio attacks sucrose but not lactose or arabinose, forms indole, and often gives a positive cholera red reaction

d **Typing of Enteric Pathogenic Microorganisms —**

There are a number of specialized laboratories which, without charge, determine the exact type of enteric microorganisms which are found in these specimens These laboratories are called "Salmonella Centers" or "Enteric Centers" At the present time this author knows of the following enteric centers in America

U S Salmonella Center (Director Dr P R Edwards), Communicable Disease Center, Atlanta 3, Ga

National Salmonella Center (Director Dr F Seligmann) Beth Israel Hospital Stuyvesant Park East, New York, N Y

Laboratories of the State Department of Health (Director Dr F I Mickle), Main Street, Hartford Conn

Dr W R Hinshaw, Department of Veterinary Medicine University of California Davis, Calif (Main interest Salmonellae of avian and reptile origin)*

Dr Oscar Felsenfeld, Cook County Hospital, Chicago, Ill

Dr E Hormaeche, Instituto of Public Health, University of Montevideo, Uruguay

*Recent address Camp Detrick Frederick Md

Dr A Varela, Institute of Public Health and Tropical Medicine, Mexico City, Mexico
Dr J H Monteverde, Institute of Infectious Diseases, School of Veterinary Medicine, University of Buenos Aires, Argentina
Dr Luis M González, School of Tropical Medicine, San Juan, Puerto Rico

APPENDIX

Outline for Enteric Surveys in the Tropics

A Medical field workers, with little experience in this type of work, general practitioners, nurses, etc, collect stools into an outfit consisting of

1 One bottle containing 10 per cent formalin or D'Antoni's iodine, and,
2 One bottle containing glycerin saline preservative

A_1 Veterinary field workers mail suspected material—stools, pus viscera, etc—in an outfit consisting of

1 One bottle containing 10 per cent formalin, and
2 One bottle containing glycerin saline preservative

A_2 Sanitary engineers mail water, food, and milk samples, without preservative, to the central laboratory (See D)

B Intermediate laboratories with semiskilled personnel, but under the supervision of a bacteriologist

1 Streak the material from glycerin saline preservative to plates, pick colonies, and mail such transplants to central laboratory (See D)
2 If fixed slides for protozoa are prepared, carry out the staining of these slides and mail them to central laboratory

C. Hospital and clinical laboratories collect stools from the sick and examine them directly for parasites, prepare hematoxylin stained slides,* and carry out flotation methods, streak stools on media, pick colonies and mail to central laboratory

D Central laboratory, headed by specialist in enteric work with skilled bacteriologists and parasitologists

1 Examines preserved material and permanent slides, if necessary,
2 Studies cultures received from other laboratories
3 Examines veterinary and sanitary material,
4 Keeps evidence of enteric cases and carriers, and
5 Makes final reports to the public health authorities

I Public health authorities

1 Designate areas for surveys,
2 Take steps to insure proper treatment and isolation of the sick and of carriers, and
3 Coordinate the work of physicians, veterinarians, sanitary engineers, and public health workers to combat the infections

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*For this purpose Schaudinn's fluid is preferred.

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CHAPTER 72

LABORATORY METHODS IN THE DIAGNOSIS OF HELMINTHIASES

FRANCISCO J AGUILAR

INTRODUCTION

In the diagnosis of parasitic diseases Kouri and his collaborators (1943) called attention to two methods of laboratory investigation the *direct* by which one views the parasite or the elements derived from it to obtain an *absolute* diagnosis and the *indirect* or investigations of the cytologic and humoral reactions of the patient eosinophilia the presence of antibodies allergy etc to obtain a *presumptive* diagnosis

DIRECT METHODS OF DIAGNOSIS OF HELMINTHIASES

A simple *macroscopic* view is sufficient in many cases to make the diagnosis. In other cases because the parasites are very small it is necessary to use magnification either a simple hand lens or a fully equipped microscope with high magnification

At times the parasites are present in such small numbers that concentration methods either mechanical or biologic are used The mechanical methods of concentration consist most often of centrifuging and depend upon the physical nature of the material as density of eggs The biologic methods concentrate the parasites actively by using their natural hydrotropism thermotropism or phototropism by permitting them to multiply in artificial culture media, or by transferring them to the intermediate hosts where they multiply and concentrate (xenodiagnosis)

I Examination of Stools

A. COLLECTION OF THE SPECIMEN

Recently passed stools must be collected in clean widemouthed sterile glass receptacles* No antiseptics should be added Avoid mixing the feces with urine since urine alters the viability of the parasites The stool must be protected from insects especially flies

Certain authors suggest that the stool should be obtained after a laxative such as magnesium sulfate In the event that the examination is negative, it may be necessary to make repeated examinations of as many as 8 to 10 specimens The first day s specimen should be spontaneously passed then specimens are obtained alternately first after a laxative then another without the laxative, next with the laxative and so on

*Editor s note (O F) In the United States, cardboard containers are frequently found satisfactory and are easy to dispose of

Certain helminths cause lesions around the anal orifice, accompanied by itching. In the presence of such symptoms, search the stools for *Enterobius vermicularis, Taenia saginata, Inermicapsifer cubensis,* or *Dipylidium caninum*.*

B TECHNIC OF HELMINTHOLOGIC EXAMINATION OF THE STOOL

1 **Macroscopic Examination**.—This is a search for parasitic elements without the aid of a microscope, for female *E vermicularis*, gravid segments of *T saginata, I cubensis, D caninum*, etc. When such elements are seen in the stool specimen, they should be separated and a simple hand lens or a compound binocular microscope should be used. In dealing with liquid or pasty stools, it may be necessary to use a screen to sift out the parasitic elements.

2 **Microscopic Examination**.—In a routine examination of feces for eggs or larvae of helminths, make an unstained preparation on a microscopic slide using a thick portion of the feces. Then make a finer preparation, and last, one from the screened and centrifuged sedimented portion. Also examine a preparation made after concentration with a low density fluid, such as that of Telemann, or Carlos and Barthelmy. If looking for protozoa at the same time, use Lugol's solution† or make a Gram stain, or, in some cases, use the iron hematoxylin method.†

3 **Preparation of a Fresh Specimen for Microscopic Examination (Method of Kouri)**.—With a wooden applicator, toothpick, or platinum loop pick up a piece of fecal material about the size of a grain of rice.

Holding the slide in the left hand, place a particle of stool in the center of the slide.

Place a drop of saline on the fecal matter and mix with the applicator. This is a fresh thick preparation.

A finer fresh preparation can be easily made from the thick portion by absorbing the excess fluid with filter paper placed at the edge of the cover glass, adding water, and at the same time exerting very gentle pressure with the finger, in a rotary manner, in the center of the cover glass.

To stain, place a drop of Lugol solution over the drop of fecal suspension in the center of a slide, mix with the applicator, and cover with a cover glass. Donaldson iodide iodine and eosin solution can be used in place of Lugol if preferred.*

C CONCENTRATION OF EGGS OF HELMINTHS

1 **Water Centrifugalization**.—Mix 1 to 10 Gm of fecal matter with 10 to 20 times its volume of water. Pass the mixture through 2 layers of fine gauze and collect the filtrate in 1 or 2 centrifuge tubes.

Centrifuge at 2,500 r p m for 3 to 5 minutes.

Decant the supernatant fluid and examine the sediment under high and low power. This method serves to concentrate eggs of *Fasciola hepatica* and nonfertile eggs of *Ascaris lumbricoides*.

2 **Lane Direct Centrifugation Method**.—Place a small amount of feces in a special test tube and mix with tap water.

Centrifuge for 1 minute at 1,000 to 1,200 r p m and decant. Repeat the washing if necessary.

Fill the tube with saturated solution of sodium chloride (sp gr 1 19) and top with an 18 by 18 mm, No 3 cover glass. Be sure that the surface film touches the cover glass.

Centrifuge 1 minute.

Lift the cover slip straight upward and mount on a glass slide.

3 **Method of Willis and Malloy**.—See Gradwohl and Kouri (1948), Vol III, p 46.

4 **Acetic Acid Ether Method**.—Suspend about 1 or 2 Gm of fecal material in about 10 c c of 5 per cent solution of acetic acid in a test tube, and shake thoroughly for a few seconds.

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*Editor's note (O F) The examination of material collected through an anal swab is preferred in such cases.

†Editor's note (O F) Different opinion is expressed in Chapter 71.

Allow to stand for 30 seconds to permit the heavy particles to settle to the bottom of the tube

Filter through a single or double layer of gauze and collect the filtrate in a test tube The tube should be one third full

Add an equal volume of ether, stopper tightly with a rubber stopper, and shake vigorously, about 15 to 30 seconds, to obtain a thorough mixture

Immediately centrifuge for 2 3, or 5 minutes to separate the material into 4 well marked layers The topmost layer is the ether extract Immediately below this is a plug of detritus, composed of coarser particles proteins, and soap The acid solution is below this plug, and a small amount of sediment is at the bottom of the tube

The 3 upper layers can easily be removed by a gentle jerk of the tube, leaving the sediment adhering to the bottom of the tube if this is done gently

Collect the sediment with a capillary pipette and place on a slide Cover with a cover glass and examine microscopically The material may also be fixed and stained.

This method gives a much higher degree of concentration than do many other methods

5 **Method of Telemann and Rivas**—Place in a test tube 10 c c of a 5 per cent acetic acid solution and add 1 or 2 Gm of feces Stopper with a cork and shake thoroughly to render the contents homogeneous

Allow to stand for 1 minute to sediment the thicker particles then filter through 2 layers of fine gauze Collect the filtrate in a centrifuge tube

Mix the liquid filtrate with equal parts of sulfuric ether

Stopper the tube and mix the contents

Centrifuge at 2,500 r p m for 5 minutes The material separates into 4 layers a top layer of ether, a layer of residue, a layer of acid and a small quantity of sediment at the bottom of the tube

Decant the upper portion then pick up the sediment from the bottom of the tube using a capillary pipette Examine under high and low powers

This method concentrates the eggs of helminths but has the objectionable feature of destroying protozoan cysts

6 **Method of Faust (Zinc Sulfate Flotation)**—See Chapter 71 and Gradwohl and Kouri (1948)

This is the most efficient method thus far devised for concentration of protozoan cysts from feces It is satisfactory as brine flotation for helminth eggs, and it also floats live Strongyloides larvae (Faust, 1939)

7 **Loughlin and Spitz Method for Concentrating Helminth Eggs and Protozoan Cysts (Saline Aerosol Ether Xylol)**—Measure 4 c c of feces into a dilution counting flask which has been filled to the 56 c c mark with isotonic sodium chloride solution

Add 8 drops of laboratory aerosol

Add several glass beads (6 mm), and after giving the mixture an initial shaking, set aside in a refrigerator for several hours or overnight Remove and complete the comminution of the feces by vigorous shaking assuring adequate distribution of the eggs throughout the fecal suspension

Transfer 1 5 c c of the suspension immediately to 15 c c conical centrifuge tube

Add 3 5 c c of isotonic sodium chloride solution, 5 c c of ether, and 2 drops of xylol Place a rubber stopper in the tube and shake for 30 seconds.

Centrifuge at 2,000 r p m for 1 5 minutes and allow the centrifuge to come to a stop gradually without interference

Separate the floating coagulum from the walls of the tube with a thin wooden applicator

Decant quickly, without disturbing the sediment in the bottom of the tube, then, while holding the tube almost horizontal, clean off any coagulum adhering to the inside of the tube with an applicator covered with gauze

Add 1 or 2 drops of isotonic sodium chloride solution to the sediment and mix thoroughly with a capillary pipette

Transfer the entire suspension to a 1 5 by 3 inch (3 8 by 7 6 cm) *glass slide and* cover with a 22 by 30 mm cover glass

Examine the entire preparation for eggs Those found are from 0 1 Gm of the original fecal specimen

The Stoll displacement flask, although preferred, may be replaced by any container similarly marked A little caution in decanting is necessary in order not to disturb the sediment Protozoan cysts may be stained with iodine solution

When eggs are demonstrated, the contents of the displacement flasks may be used for dilution counting without any additional preparation

8 **Baroody Method (Modification of the Faust Method for Concentration of Cysts and Eggs)** —See Gradwohl and Kouri (1948)

9 **Baroody and Most Water Centrifugal Method for Demonstrating Schistosoma Japonicum Eggs** —See Gradwohl and Kouri (1948)

D COUNTING HELMINTH EGGS

Counting helminth eggs is not a practical routine test, but it is useful to give an approximate idea of the intensity of parasitic infestation

1 **Method of Stoll** —See Gradwohl and Kouri (1948), Vol III, p 45

2 **Method of Caldwell and Caldwell** —This is a combination of the technics of Willis and of Stoll Thirty per cent antiformin solution is used

Sirup is made from cane sugar (density 1 230) by adding 750 Gm of sugar to 1,000 c c of distilled water

In a tube or flask graduated to 40 c c, place a mixture of 4 Gm of stool and 4 c c of Antiformin solution

Mix with a glass rod

Keeping the rod in the tube or flask, place in the incubator at 37° C for 1 hour

Add 32 c c of the sirup, and mix the 2 fluids

Introduce a serologic pipette to the bottom of the tube, covering the upper opening so that some air is trapped in the pipette, and withdraw 0 1 c c of the suspension from the bottom of the tube

Place the mixture on a slide and spread it into a rectangle It is not necessary to use a cover glass

Count the number of eggs under the microscope, using the low magnification

Calculation —The number of eggs counted times 100 gives the number of eggs per gram of fecal material If 0 2 c c instead of 0 1 c c was extracted, multiply by 50 instead of by 100

If eggs are not found, place the total suspension in another flask and allow it to remain for 20 minutes, then place some of the pellicle on a slide

3 **Hamburg Cover Glass Method** —This method, devised by Hung and Fulleborn, makes use of saline flotation for increasing the yield of eggs, and provides a certain accuracy without the time consuming labors of the Lane method

Use a special glass or metal cylinder about 5 cm in diameter and 3 5 cm in height, provided with a depression in the bottom which will hold 1 Gm of formed feces

Fill the container almost to the top with concentrated salt solution, and mix thoroughly

Carefully place three 18 mm square cover glasses on the surface and allow them to remain for 10 minutes

Place the cover glasses on glass slides

Count all the eggs in these 3 areas and average the counts

Compute the total number of eggs in the specimen by multiplying the count by 7 0 *if the eggs* number 20 to 40, by 7 5 if they number 40 to 70, by 8 5 if they number 70 to 90, and by 9 5 if they number 90 or more (Faust, 1939, Gradwohl and Kouri, 1948)

Conclusions—Methods of counting eggs permit one to establish the relationship between the number of parasites in the intestines and the number of eggs found in the stool. The figures vary greatly according to the author and the method (Stoll, Hill, Soper, Cort, Augustine, Nazmi Helmy, MacGavran and Manalang) as well as upon conditions and consistency of the stool.

Hirai has given the following formulas for Ascaris:

Eggs per mg × 100 – 2 770 = number of females

Number of females × 4 5 – 5 5 = number of males

In Table XXXV Zschucke (1931) are given figures for pasty stools (Langeron 1942)

TABLE XXXV

NUMBER OF EGGS PER GRAM OF FECES	ANCYLOSTOMA DUODENALE	NECATOR AMERICANUS	ASCARIS LUMBRICOIDES	TRICHURIS TRICHIURA
1 Per female	125	50	1 000	5
2 Per helminth	6		600	4

According to the second figure the calculation for Ancylostoma and Ascaris shows a proportion of females to males of 1 1 while for Trichuris 1 17.

For stools of various consistencies the following coefficients are given as to the number of eggs found: solid stools 0 5, semisolid stools 0 [illegible], semiliquid stools 1 5 and liquid stools 2 0.

Earl and Doering (19[illegible]2) concluded that the logarithm of the figure obtained in an exact enumeration represents exactly the normal distribution. There is therefore a correlation between the logarithm of the count obtained in a mixture of stools and the logarithm of the total number of helminths expelled since treatment began.

E NEGATIVE EXAMINATION

With respect to the diagnosis of helminthiasis a negative examination is always subject to doubt (Langeron 1942) because parasitism can exist without manifesting itself by the presence of eggs in the stools:

1 When only male nematodes are present.

2 When there are only larvae of cestodes or young nematodes.

3 When the females are infertile.

4 By reason of the fact that there are negative periods for expulsion of helminth eggs.

5 When the parasites do not produce eggs in the intestines (Taenia, Enterobius, etc.)

F DIAGNOSIS OF SPECIAL CASES

1 **Schistosomiasis Mansoni.**—In formed stools eggs can be found in the bloody mucus. Khalil and Salah El Din use a conical glass with saturated salt solution. Eggs of Ancylostoma float on top, in the bottom of the flask they found eggs of Schistosoma.*

*Editor's note (O F) The acid ether flotation technic and rectal biopsies are frequently helpful.

2 **Enterobiasis —**

a *Finding the Oviferous Female* —Sometimes the female parasites can be seen in the excreta, or an intense pruritus, exaggerated at night, is present Examination of the anal region reveals the parasites The oviferous females are brought to the laboratory in water or in alcohol If they are in a dry state, they are retracted, desiccated, but contain typical asymmetrical eggs

b *Microscopic Examination of the Scrapings From the Anal Margins* —

(1) *Hall tube (NIH swab)* This method was developed at the National Institute of Health in Washington, D C, by Hall and collaborators (Wright, Jones, Cram, Nolan) It consists of a piece of Cellophane wrapped around the end of a glass rod, and bound down by a rubber band This is carried in a glass tube

In the morning, before washing, the margins of the anus are rubbed with this Cellophane The swab is introduced into the container and sent to the laboratory The rubber band is removed and the Cellophane examined after the addition of 2 drops of saline

(2) *Method of Graham* The method of Graham consists of placing a narrow strip of transparent, gummed cellulose tape (Scotch tape), about 8 cm long, over the anal area, then transferring it to a microscopic slide If eggs are present, they will adhere to the paper and be readily seen under the microscope

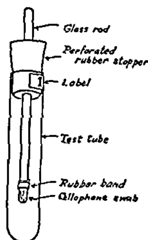


Fig 471 —The NIH swab (Hall)

(3) *Graham Mazzotti method* A piece of transparent gummed cellophane paper (Scotch tape) is doubled over the rounded end of a wooden tongue depressor, cut in half, so that the glued surface is turned outward The ends of the tape are doubled back toward the inside, about 0 5 cm, so that the Scotch tape will adhere to the tongue depressor The specimen is collected by holding the wooden depressor in the right hand, as shown in Fig 472, while the anal opening is separated by the left hand The paper is then rubbed from one side to the other over the anal margin, with the cellophane end of the tongue depressor The paper is then put on a slide

If one wishes to preserve these swabs before examining, they can be placed in an accordion pleated piece of thick waxed paper covered with talcum to keep the tape from sticking to the paper

Eggs of *Taenia saginata Hymenolepis nana, Trichuris trichiura,* and *Ascaris lumbricoides can also be isolated occasionally in this way* (Wyss, 1946)

c *Microscopic Examination of the Mucosa or Scrapings From Subungual Grooves* — Eggs of Enterobius can be found by examining the subungual grooves

d *Direct Examination of the Anus* at times permits finding the oviferous female

e Examination of the Feces—Macroscopic and microscopic examinations as well
centration can be used

3. **Ancylostomiasis (Method of Clayton Lane)** (Direct centrifugal flotation)—
sify 1 Gm of feces in water and centrifuge
Dilute the sediment in 18 c c of saturated solution of sodium chloride
Centrifuge in a tube with a flat bottom, covered with a cover glass 0.5 mm t
held in place by clamps The eggs will come to the top where they cling to the co
glass

Lift the cover glass and examine it as a hanging drop preparation by placing 2 of
corners over 2 small masses of Plasticine

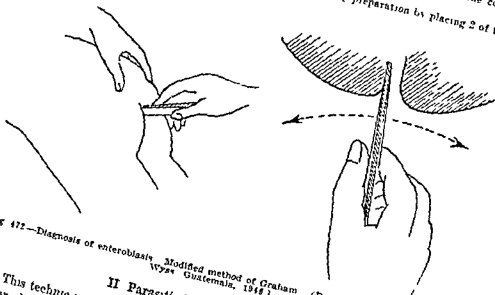


Fig 472—Diagnosis of enterobiasis Modified method of Graham (Reproduced from Nicholls
Wyss Guatemala, 1946)

II Parasitic Examination of Bile

This technic is used largely for the diagnosis of human fascioliasis as well
as for clonorchiasis, strongyloidiasis necatoriasis, ancylostomiasis biliary as
cariasis giardiasis, and amebiasis

**Technic of Kourí for Examination of Bile Obtained by Duodenal Intubation in the
iagnosis of Certain Types of Duodenal-Jejunal Parasitism.—**

Equipment Cylinders graduated to 500 and 1 000 c c Petri dishes 20 cm in diameter
duates, centrifuge tubes, pipettes, watch glasses, slides and cover slips, microscopes,
ocular and dark field, with natural or artificial light

Method Pour the bile into a Petri dish over a white background
Note the macroscopic characteristics of the bile especially whether or not there is mucus
f there is any movement in the fluid Place the Petri dish alternately over a white and
background
ellow or brownish mucus contains eggs in large quantities whereas light colored mucus
does not show eggs Use a short pipette of wide caliber to pick up any suspicious
akes Put these flakes in a watch glass for microscopic examination
amine all the floccules in the watch glass, microscopically after centrifuging and
by decanting and repeated centrifuging Examine the material in the watch glass
power If a binocular stereoscopic microscope is available a direct examinat
le of the material in a Petri dish

2 **Enteroblasts —**

a *Finding the Oviferous Female* —Sometimes the female parasites can be seen in the excreta, or an intense pruritus, exaggerated at night, is present Examination of the anal region reveals the parasites The oviferous females are brought to the laboratory in water or in alcohol If they are in a dry state, they are retracted, desiccated, but contain typical asymmetrical eggs

b *Microscopic Examination of the Scrapings From the Anal Margins* —

(1) *Hall tube (NIH swab)* This method was developed at the National Institute of Health in Washington, D C, by Hall and collaborators (Wright, Jones, Cram, Nolan) It consists of a piece of Cellophane wrapped around the end of a glass rod, and bound down by a rubber band This is carried in a glass tube

In the morning, before washing, the margins of the anus are rubbed with this Cellophane The swab is introduced into the container and sent to the laboratory The rubber band is removed and the Cellophane examined after the addition of 2 drops of saline

(2) *Method of Graham* The method of Graham consists of placing a narrow strip of transparent, gummed cellulose tape (Scotch tape), about 8 cm long, over the anal area, then transferring it to a microscopic slide If eggs are present, they will adhere to the paper and be readily seen under the microscope

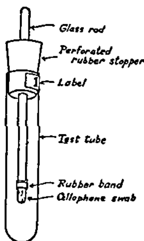


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If one wishes to preserve these swabs before examining, they can be placed in an accordion pleated piece of thick waxed paper covered with talcum to keep the tape from sticking to the paper

Eggs of *Taenia saginata, Hymenolepis nana, Trichuris trichiura,* and *Ascaris lumbricoides* can also be isolated occasionally in this way (Wyss, 1946)

c *Microscopic Examination of the Mucosa or Scrapings From Subungual Grooves* — Eggs of Enterobius can be found by examining the subungual grooves

d *Direct Examination of the Anus* at times permits finding the oviferous female

c Examination of the Feces—Macroscopic and microscopic examinations as well as concentration can be used

3 **Ancylostomiasis (Method of Clayton Lane)** (Direct centrifugal flotation)—Emulsify 1 Gm of feces in water and centrifuge

Dilute the sediment in 18 c c of saturated solution of sodium chloride

Centrifuge in a tube with a flat bottom, covered with a cover glass 0 5 mm thick, held in place by clamps The eggs will come to the top where they cling to the cover glass

Lift the cover glass and examine it as a hanging drop preparation by placing 2 of the corners over 2 small masses of Plasticine

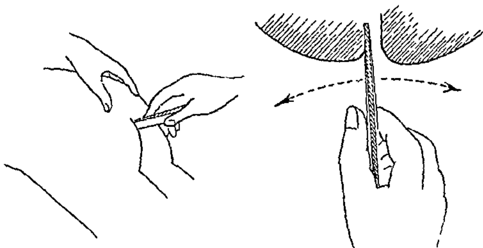


Fig 472—Diagnosis of enterobiasis Modified method of Graham (Reproduced from Nicholás Wyss Guatemala 1946)

II Parasitic Examination of Bile

This technic is used largely for the diagnosis of human fascioliasis as well as for clonorchiasis strongyloidiasis necatoriasis ancylostomiasis, biliary ascariasis giardiasis, and amebiasis

Technic of Kouri for Examination of Bile Obtained by Duodenal Intubation in the Diagnosis of Certain Types of Duodenal-Jejunal Parasitism.—

Equipment Cylinders graduated to 500 and 1,000 c c Petri dishes 20 cm in diameter graduates, centrifuge tubes pipettes, watch glasses slides and cover slips microscopes, binocular and dark field, with natural or artificial light

Method Pour the bile into a Petri dish over a white background

Note the macroscopic characteristics of the bile especially whether or not there is mucus and if there is any movement in the fluid Place the Petri dish alternately over a white and a dark background

Yellow or brownish mucus contains eggs in large quantities whereas light colored mucus usually does not show eggs Use a short pipette of wide caliber to pick up any suspicious mucus flakes Put these flakes in a watch glass for microscopic examination

Examine all the floccules in the watch glass, microscopically, after centrifuging and washing by decanting and repeated centrifuging Examine the material in the watch glass under low power If a binocular stereoscopic microscope is available, a direct examination can be made of the material in a Petri dish

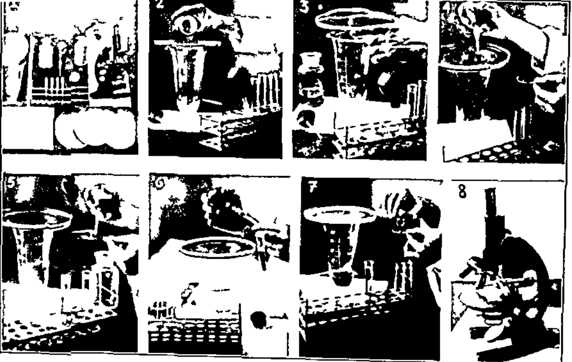


Fig 473.—*Fasciola hepatica*. Kourí's method *of examination of bile* obtained by duodenal intubation.

1 Materials: 500 to 1000 cc. graduated beaker, 20 cm. Petri dishes, brick mold, centrifuge tubes, pipettes, watch glasses, slides and cover glasses, microscope, substage lamp, black and white paper.

2 Step 1. Pour bile into Petri dish on a beaker which is over a piece of white paper.

3 Step 2. Observe macroscopic characteristics of bile, particularly the appearance of the suspended mucus. Move the Petri dish alternately over the black, then the white background.

4 Step 3. Brown or yellow *mucus* contains numerous eggs, *white mucus none*. *With* a short large bore pipette attached to a large bulb suck *up the suspected* mucus flakes, and transfer to a watch glass or slide.

5 Examine microscopically. The eggs are found in greater numbers in the center of the watch glass.

6 Step 4. Transfer all flakes to a centrifuge tube.

7 Step 5. Wash all flakes, centrifuge, decant the supernatant fluid, and examine microscopically in the watch glass.

8 Step 6. Place the watch glass with the flakes on a slide and examine with low power. If a binocular dissecting microscope is used, examine directly in the Petri dish.

Examination *of oviferous* flakes (Kourí) usually provides evidence of infestation. This method may be used in clonorchiasis, lambliasis and strongyloidiasis and is valuable in necatoriasis, ancylostomiasis and biliary ascariasis.

(From Gradwohl and Kourí: Clinical Laboratory Methods and Diagnosis, ed. 4, vol. III, St. Louis, The C. V. Mosby Co.)

III Parasitic Examination of Blood and Lymph

(For filariasis and schistosomiasis hepatica)

Filariasis

Microfilariae may be found in the peripheral blood if they are present in moderate numbers, by direct examination between cover glass and slide, or by using concentration methods

1 **Direct Method Using Unstained Material**—Puncture the finger or the ear lobe and place a drop of blood on a slide Cover immediately with a cover glass and examine microscopically with low magnification Microfilariae show typical movement

2 **Examination of Stained Blood**—Obtain blood by puncture of the finger or ear lobe and make a thick drop preparation Let dry in the air

Cover the slide with 1 per cent acetic acid solution for 1 minute to dehemoglobinize Fix in methyl alcohol and stain by the Giemsa method *

3 **Stubli's Concentration Method**—

Material—Three per cent acetic acid solution Giemsa stain, 1 drop of stock stain in each c c of neutral distilled water

Technic—Obtain 5 c c of blood by venous puncture and add immediately to 10 to 15 volumes of 3 per cent acetic acid

Shake rapidly to prevent coagulation

Centrifuge for 3 to 5 minutes at 1 500 r p m

Decant the supernatant fluid and take a drop of the sediment for direct examination Examine under low power

Stain the remaining sediment with Giemsa stain or with hematoxylin eosin after removing *all the acetic acid by washing with large quantities of neutral distilled water*

4 **Adults and Embryos**—Adults and embryos are found in the respective tissues See Chapters 39 and 40

IV Helminthologic Examination of Exudates, Cystic Fluids, and Spinal Fluid

A. EXUDATES

Examination of the exudates of the different serosae (pleural peritoneal pericardial, tunica vaginalis) will in some cases establish an etiologic diagnosis of helminthiasis It is best to make an immediate examination before the fibrin has coagulated (Widal and Ravaut) The fibrin clot may be more or less apparent and voluminous according to the case but it always forms within several hours or several minutes The fibrin mesh will gather in a great number of parasitic elements so that it is best to examine the specimen before the clot forms

1 **Direct Examination of Unstained Material**—If the liquid is very thick, syrupy or purulent, dilute it with a drop of saline after it has been placed on a slide Cover with a cover glass and observe under a microscope

2 **Direct Examination of the Unstained Sediment Obtained by Centrifuging**

3 **Examination of a Smear Prepared Like a Blood Film**—Fix this in methyl alcohol and stain with Giemsa stain

*See also Chapters 39 and 68

To prevent coagulation of the liquid, an *anticoagulant* can be added immediately upo collection of the specimen 5 per cent sodium citrate, or a solution containing 2 8 Gm of potassium oxalate in a liter of 0 85 per cent saline

Recognition of the proligerous vesicles scolices and hooklets of *Echinococcus granulosus* enables one to make a definite diagnosis of echinococcosis

B CYSTIC FLUIDS

The technic for helminthologic examination of cystic liquids is the same as that described for exudates (1) examination of the unstained material (2) examination of sediment obtained by centrifuging, and (3) examination of a smear stained like a blood smear

C SPINAL FLUID

It is possible to find forms of *E granulosus* by direct examination of the sediment obtained by centrifuging

V Helminthologic Examination of Urine

Among the helminths that can be found in the urinary sediment are

1 The microfilariae of *W bancrofti*, if they pass into the urinary passages

2 The elements of the hydatid cyst which has ruptured into the urinary passages

3 Eggs of *Schistosoma haematobium*

4 Eggs of *Dioctophyme visceralis (Eustrongylus gigas)*, a parasite which lives in the renal pelvis

VI Helminthologic Examination of Sputum

A macroscopic examination is first made, followed by a microscopic examination The mucopurulent portions particles of necrotic tissue, and any portions supposedly containing parasitic elements are selected for examination

It is possible to find in the sputum larvae of *Necator americanus, Strongyloides stercoralis, and Ascaris lumbricoides*, the eggs of *Paragonimus westermani* and *kellicotti*, and elements of hydatid cysts

VII Helminthologic Examination of the Tissues Biopsies and Histopathologic Sections

A BIOPSIES

1 Onchocerciasis —

a *Biopsy of the Skin* —Cleanse the region, the wall of the ear or the forehead, and remove a small portion of the skin adjacent to the region of the nodules with a pair of curved scissors a safety razor blade or a straight razor The cut must be made with the least possible bleeding

Transfer these fine sections of skin to slides and cover with a cover glass adding a few drops of saline solution Microscopic examination under low power will reveal the microfilariae with their characteristic movements

b *Aspiration Biopsy* —Puncture is made with a 22 gauge needle attached to a hypodermic syringe Immediately place the product obtained by aspiration on a slide and cover with a cover glass

2 Schistosomiasis Mansoni —

Biopsy of the Anorectal Mucosa —The polypoid lesions of the rectum are chosen for examination Use the usual routine histologic technic staining with hematoxylin and eosin

B HISTOPATHOLOGIC SECTIONS

See Chapters 69 and 70

The following is a résumé of the helminthiases in which definite diagnosis can be made by histopathologic sections

Nematodiases

Trichuriasis appendicitis produced by *Trichuris trichiura*

Enterobiasis appendicitis produced by *Enterobius vermicularis*

Filariasis bancrofti funiculitis produced by *Wuchereria bancrofti* and *Wuchereria malayi*

Onchocerciasis subcutaneous nodules and ocular lesions produced by *Onchocerca volvulus*

Trichinosis cysts and larvae of *Trichinella spiralis* localized in the diaphragm and other muscles

Cestodiases

Cysticercosis cerebral or other localizations due to the larval form of *Taenia solium* called *Cysticercus cellulosae*

Echinococcosis hydatid cyst (development of the larva of *Echinococcus granulosus* especially in the liver lung etc)

Trematodiases

Fasciolisis hepatica lesions produced in the biliary canaliculae by the *Fasciola hepatica*

Clonorchiasis lesions produced in the liver by the *Clonorchis sinensis*

Paragonimiasis lesions produced in the lung by the *Paragonimus westermani* and *Paragonimus kellicotti*

VIII Xenodiagnosis

Xenodiagnosis was introduced by Brumpt in 1914 It makes the diagnosis by means of natural culture of the parasite in the digestive tube of the habitual vector host or in an occasional host

This procedure is especially useful in the diagnosis of Chagas disease and the relapsing fevers as well as in the diagnosis of onchocerciasis and bancroftian filariasis

A ONCHOCERCIASIS

Xenodiagnosis in this disease was suggested by Nettel The species reputedly possible transmitters of *Onchocerca volvulus* are in America *Simulium avidum S ochraceum and S mooseri* in Africa *S damnosum* and *S neavei*

Technic —A S mulium is allowed to come to rest on the skin of the individual under examination It is preferable to wait for one that will bite in some region previously

selected which is easy to find *in the zones of greater infestation* When the Simulium has lodged on the skin a test tube or a small widemouthed flask is placed over it After it has finished sucking it passes into the tube or flask The container is then stoppered with cotton containing a few drops of chloroform which will kill the Simulium

Proceed immediately to dissect the insect, with needles over a glass slide containing a drop of saline solution Use only the abdominal segment which contains the stomach with the absorbed products The head and the thorax can be separated and searched for the latent forms because in xenodiagnosis only infections with living microfilariae are successful

B FILARIASIS BANCROFTI

Craig and Ashburn observed that the saliva of the Culex mosquito (*C fatigans*) attracts the microfilariae Kouri and collaborators used this method with laboratory bred Culex This procedure is considered by some authors as a biologic concentration method for finding microfilariae of Wuchereria

IX Experimental Inoculations

In human helminthiasis experimental inoculations are made primarily for investigative purposes

X Cultures in Vitro Natural and Artificial Media

A COPROCULTURE

Coproculture is made for the diagnosis of parasitism by *Strongyloides stercoralis Necator americanus Ancylostoma duodenale* and *Schistosoma mansoni* when the larvae of these parasites or their eggs occur in very scanty numbers in the feces

For this method it has often been recommended that the feces be mixed with animal charcoal or with pulverized earth sterilized or with a little water Kouri and collaborators obtained good results without using any of these substances They make use of the property of some larvae of being attracted toward water (positive hydrotropism) or toward light (positive phototropism) When some water is poured over the fecal mass and the specimen kept at a temperature of 28° to 32° C after a certain time *if the feces contain* larvae of ancylostomas or of strongyloides the larvae leave the feces and move toward the water where they concentrate They can be seen when a drop of this liquid *is* examined *although they could not have been found* if a direct examination of the feces had been made because of their scarcity Coproculture is therefore a method of biologic enrichment based on the *tropism of the larvae This justifies the term* "tropodiagnosis" proposed by Kouri and collaborators

B CULTURE OF THE FECES

Culture of the feces is made by inoculation of artificial media This method is used especially for the diagnosis of intestinal amebiasis and other protozooses, and will not be discussed in this chapter

PRESUMPTIVE DIAGNOSIS OF THE HELMINTHIASES

In this group there should be considered (1) serology, (2) hematology, and (3) histology

I Serologic Diagnosis of the Helminthiases

Serologic and related reactions depend on the development of a host organism reaction In helminthic infections those species of worms which are intimately associated with the host tissues, so that their by products become diffused throughout the body, are more readily diagnosed by serologic methods Thus the species of Schistosoma Echinococcus and Trichinella give a positive serologic test in a very high percentage of cases while most helminths of the intestinal tract as well as certain of the trematodes resident in the biliary passages give negative or uncertain tests

Complement fixation agglutination and precipitation tests are used in the serologic diagnosis of parasitic infections for identification of parasites

A COMPLEMENT FIXATION

The technic on the whole is similar to that of the Wassermann test for syphilis although the antigen must be either species specific or group specific

1 Schistosomiasis —The antigen may be prepared either from adult worms removed from human or reservoir hosts or from the livers of snails containing the infecting agent

a *Yoshimoto Technic* —

Alcoholic antigen Extract the dried powdered worms with 20 parts of absolute alcohol for 24 hours with frequent shaking

Centrifuge until clear

Store the supernatant liquid in ampules in an ice chest

Dilute the alcoholic extract for use with physiologic saline It may be evaporated and an aqueous solution made from the residue

Serum Inactivate patient's serum at 56° C for one half hour and use it undiluted

Complement Dilute fresh guinea pig serum just before using with 10 parts of physiologic saline

Hemolysin Prepare hemolysin in rabbits by injecting intravenously at 7 day intervals 3 to 4 injections 5 c c each of 5 per cent suspension of goat blood cells in saline

Recover the serum in the usual manner and inactivate at 56° C for 30 minutes

Dilute 1 25 immediately before using

Technic Distribute the diluted antigen in amounts of 0 2 to 0 4 c c in a series of sterilized test tubes

Add 0 2 c c of serum

Add 0 2 c c of freshly diluted complement

Shake the tubes thoroughly and place in a water bath at 37° C for 1 hour

Add 0 2 c c of diluted hemolysin and 1 c c of a 2 5 per cent suspension of washed goat corpuscles

Replace in the water bath for 2 hours

Remove and leave in a cold place overnight

Read in the usual manner

b *Fairley Technic* —

Alcoholic antigen Tease wet snail livers directly in absolute alcohol using one c c of alcohol per liver

Shake for 20 minutes

Extract for 24 hours at 37° C without shaking

Filter

Concentrate the filtrate in a water bath at 45° C by bubbling air through the solution until it becomes turbid

Add absolute alcohol slowly until the solution becomes clarified

Store in 1 c.c quantities in ampules in the ice chest

For use dilute 1 40 with physiologic saline (Belding, 1943)

Serum, complement, and hemolysin These are prepared as in the Wassermann technic

Technic is similar to that of the Wassermann reaction

Serum diagnosis is particularly valuable in suspected cases of schistosomiasis (1) during the latter part of the incubation period before the eggs are produced, (2) in chronic cases in which the walls of the intestine and bladder have become so fibrosed that eggs cannot pass from the mesenteric veins or vesical plexuses into the lumen of these organs, and (3) in unisexual infections, which may otherwise be diagnosed as "idiopathic splenomegaly" (Faust, 1939)

2 **Paragonimiasis**—The antigen used in the serologic test is a saline extract of macerated adult *Paragonimus westermani*

The test is particularly useful in suspected nonpulmonary paragonimiasis, where the worms lodge in deep foci and are not passed in the excreta or through cutaneous lesions

3 **Echinococcus Infection**—

a *Aqueous Hydatid Antigens*—The fluid from hydatid cysts in infected cattle, sheep, hogs, or man, obtained under aseptic conditions, is used for the antigen Fluid from degenerating cysts and fluid which contains blood or serum is not used

Filter the fluid through a Seitz filter

Incubate to determine sterility

Seal in ampules, and store in the ice chest This fluid retains its antigenic properties for several months

b *Alcoholic Hydatid Antigens*—Fairley prepared an alcoholic extract by grinding the scolices with fine sand, adding 9 volumes of absolute alcohol, incubating at 37° C for 2 days and using the filtrate as an antigen

Dennis (1937) added crystalline trichloracetic acid to a concentration of 5 per cent, to chilled, fresh, sterile hydatid cyst fluid obtained from sheep and cattle

The mixture is kept at 40° C overnight

The precipitate is collected, washed, and treated with dilute sodium hydroxide until the protein is completely dissolved

The protein is then reprecipitated with N/1 acetic acid, washed, dried at 37° C, ground to a powder, and stored in a desiccator, in the dark

Dennis obtained about 0 1 Gm of purified antigen from each liter of hydatid fluid

The stock antigen is diluted 1 1 000 in slightly alkalinized physiologic saline sterilized by filtering through a Seitz filter, and preserved by adding 0 5 per cent of chloroform

This solution is about 10 times as potent as the unpurified hydatid fluid

c *Dennis Antigen (The Weinberg Parvu, Ghedini and Imaz Lorentz Reaction)*—Dilute the Dennis purified antigen to make a 1 5,000 concentration

Follow the Kolmer serologic technic

The antigen is sensitive, specific, not anticomplementary, and does not give false positive reactions (Faust)

4 Trichinosis —

Antigen (Strobel, 1911) —Tissue containing the trichinas is digested in an incubator for 24 hours, with sodium hydroxide and antiformin It is later neutralized with hydrochloric acid filtered and kept for 14 days in a refrigerator This provides a reliable antigen

5 Fascioliasis, Taeniasis Saginata, Ascariasis, Ancylostomiasis, and Onchocerciasis —The complement fixation tests are in the experimental stages but at present are not in general use

B PRECIPITIN REACTION

1 Echinococcus Infection —

The Felg and Lisbonne Reaction —Obtain fresh hydatid fluid aseptically from infected sheep

Preserve by adding phenol solution This antigen remains stable for several months

Add 0 5 c c of fresh serum from the patient to an equal quantity of the antigen in small agglutination tubes

Allow to stand for 36 hours at room temperature

In sera with high precipitin content a precipitate forms within 2 or 3 hours Heavy flocculation is designated as ++ fine precipitate with granules in suspension as ++ and microscopic granules as + and no precipitate or microscopic granules as −

2 Cysticercus Cellulosae —

The test is made in the same manner as when testing for hydatid infection using as antigen the fluid obtained from Cysticerci from previous cases of human beings or more practically from the bladder worms of *Taenia solium* or other species of Taenia the larvae of which develop in hogs rabbits and other intermediate hosts (Faust)

3 Trichinosis —

Sawit Technic (1937) —

Antigen Digest 80 Gm of muscle from an infected rat in 1 500 c c of 0 6 per cent pepsin in 0 3 per cent hydrochloric acid solution at 37° C for 5 to 12 hours shaking from time to time

Strain through 6 layers of cheese cloth

Dilute with an equal amount of water and allow to stand for 2 hours in a sedimentation glass

Siphon off the upper third of the liquid and replace with tap water

Repeat 6 to 8 times until the supernatant fluid is clear

Allow the purified material to remain in the sedimentation glass overnight Then place it in a Petri dish and allow to dry

Transfer to a beaker and treat with ether for 24 hours

Remove the ether and dry the residue in vacuo over sulfuric acid for 48 hours

Pulverize the dry residue in a mortar and store in sterile ampules

Dissolve in Coca s solution 1 Gm to 100 c c, to make the stock solution

Store in an ice chest

Dilute 1 50 for intracutaneous tests giving a final concentration of 1 5 000 (Belding 1942)

Coca s solution

Sodium chloride	0 5 Gm
Sodium bicarbonate	0 275 Gm
Phenol	0 4 Gm
Distilled water	100 c c

Technic Place serologic tubes in a rack and label in series of 8 tubes *(1 to 8)*
Place 0 2 c c patient s serum in each of the first 6 tubes
Place 0 2 c c of normal serum in the seventh tube
Place 0 2 c c of rabbit serum known to give a positive reaction in the eighth tube
Dilute the antigen 1 100 1 200, 1 400, 1 800 1 1600 Add to the tubes as follows by overlaying the antigen on the serum

Tube	1	2	3	4	5	6	7	8
0 2 c c of antigen diluted	1 100	1 200	1 400	1 800	1 1600	--	1 100	1 100

Add 0 2 c c of Coca's solution without the antigen to the sixth tube as a control
Negative sera remain clear *Positive sera* develop a white ring at the point of contact within 30 minutes and the antigen usually becomes cloudy white (Faust)

C INTRADERMAL REACTION

Persons infected with *animal parasites may develop hypersensitiveness* against the proteins and other products of the parasites Interdermal injection of extracts made from tissue of the parasites or from fluid elaborated by the parasite are used as well as skin tests made by placing desiccated powdered tissue of the parasite on skin which has been previously scarified Two types of positive reaction may be observed the immediate and the delayed reaction

Immediate Reaction —The immediate reaction consists of an erythematous wheal which rapidly increases in size, and which tends to extend by pseudopodial projections until it reaches a maximum size in 15 to 20 minutes and begins to fade within 1 hour

Delayed Reaction —The delayed reaction consists of an area of erythema and induration around the site of injection or application of the antigen

1 **Echinococcus Infection** —

The Casoni Reaction —Positive results with this test are reported as 80 to 100 per cent (Lemaire, Deve Bacigalupo and others)

Hydatid fluid is used as antigen

Obtain the hydatid fluid by aseptic puncture of hydatid cysts removed from the lungs and liver of sheep oxen pigs or human beings

Filter and incubate to determine sterility

Place in sealed ampules and store in ice chest It will retain its potency for 6 months (Faust)

Disinfect the skin of the arm above the elbow with alcohol

Inject 0 2 c c of the antigen intradermally

Inject 0 2 c c of physiologic saline several centimeters above this injection, or on the opposite arm as a control

The reaction is immediately positive even in infections where the cyst has proved to be suppurative or degenerative upon surgery

The test is particularly valuable in *preoperative cases*

2 **Cysticercosis Cellulosae** —The antigen is obtained from fluid in various species of Cysticerci in domestic animals It is a group specific test

The technic is carried out as for suspected hydatid disease (Faust)

3 **Schistosomiasis** —The antigen is obtained from mollusks infected with mammalian schistosomes *It may be obtained in a more purified state from adult schistosomes* removed from experimentally infected laboratory mammals

A 0 5 per cent saline extract of dried livers of the infected mollusk is used This is sterilized by passing it through a Seitz filter It is stored in ampules in the ice chest Fairley and Williams, and Talafierro, use 0 025 c c of a 0 5 per cent saline extract for the test

This reaction is a s histosoma group reaction

4 **Trichinosis** —The Bachman and Sawitz antigen (see precipitin test) is used in this test

Dilute the stock solution 1 50, making a 1 5 000 dilution

Store on ice until used.

Inject 0 1 c c of antigen intracutaneously into the forearm

Inject 0 1 c c of saline intradermally into the other arm

Positive reactions show small white swellings immediately surrounded by an unraised irregular erythematous area of about 5 cm in diameter The reaction is at its maximum in about 10 minutes and begins to fade in 15 or 20 minutes There is no reaction in negative cases The test is particularly valuable in mild cases with only vague symptoms (Faust)

5 **Filariasis** —The antigen for this test is made from the dog heart worm, *Dirofilaria immitis* The live specimens are freed of blood and serum and washed in distilled water

They are then dried the lipoids removed, and the worms dried again

After pulverizing the worms 200 parts of Coca s solution or physiologic saline are added to each 1 part by weight of the powder For *Wuchereria bancrofti* use 0 25 c c of a 0 1 per cent solution

Antigen for filariasis due to *Onchocerca volvulus* and *Loa loa* is obtained from the adult worms The reaction occurs immediately It is characterized by a diffuse erythema wheal formation and pseudopodial extensions covering an area of not less than 2 cm Accuracy of this test is at least 90 per cent (Faust)

D PHYSICAL CHANGES IN THE SERA

1 **Ascoli Miostagmin Reaction** —In some helminthiases such as hydatidosis and ancylostomiasis there is a decrease in the surface tension of the patient s serum with a corresponding increase in the number of drops of serum when the temperature and volume are kept constant using the Traube stalogmometer A mixture of antigen (hydatid fluid) and antibody (patient s serum) shows a decrease in surface tension and a resulting increase in the number of drops over the number produced by a corresponding mixture of the antigen with normal serum The name ' miostagmin meaning fewer drops is given to this reaction

2 **Erythrocytic Sedimentation Rate** —The sedimentation rate is markedly accelerated in hydatidosis and necatoriasis

II Cellular Reactions

Changes in the blood picture (anemia and particularly eosinophilia) and cellular reactions of the tissues (inflammatory reactions hyperplasia and neoplasia) can be observed in parasitic diseases in general and in helminthiases in particular, although these changes are not of a specific character

See Chapter 68 for blood changes in helminthiases

Tissue Reactions

1 **Inflammatory Reactions.**—The tissues in the presence of aggressive parasites, show connective tissue vascular reaction with infiltration of inflammatory cells Lymphocytes or plasma cells or polymorphonuclear neutrophiles predominate, usually local eosinophilia is observed At times, especially

in chronic processes, with proliferation, epithelioid cells are observed, with giant cell formation The organism tends to localize the parasite by formation of a fibrous capsule Sometimes this becomes infiltrated with calcareous salts, imprisoning the parasites It is not known whether calcification follows death of the parasite or whether death of the parasite is caused by calcification (Kouri et al, 1943)

This inflammatory phenomenon can be observed in cysticercosis, trichinosis, and echinococcosis In echinococcosis, in addition to the giant cells, echinococcic granulomata are formed

2 **Metaplastic Reactions**—Metaplasia is the transformation of one cellular type of tissue into another of the same or different type, connective or epithelial A typical example is found in pulmonary distomatosis by *Paragonimus westermani*, where transformation of the cylindrical epithelia of the bronchi into stratified pavement epithelia is noted

3 **Hyperplastic Reactions**—In hyperplasia the epithelial and connective tissues are hypertrophied, producing an excess of epithelial tissue, generally with glandular formation, with concomitant increase in connective tissue (Kouri et al, 1943)

In hepatic distomatosis, there is hyperplasia with formation of biliary adenomata, and in schistosomiasis hyperplasia in which bladder and rectal adenomata are observed

4 **Neoplastic Reactions**—Several authors have shown malignant transformation of biliary adenomata in distomatosis hepatica by *Clonorchis sinensis* and *Opisthorchis felineus* (Katsurada Askanazy, Kouri et al)

In schistosomiasis haematobia, bladder papillomata can be transformed into cancers of the bladder (Albarran and Leon Bernard, 1897)

Finally, it is necessary to show the carcinomatous reaction produced by *Gongylonema neoplasticum* and the sarcomatous reaction produced by *Cysticercus fasciolaris*, parasitic helminths of rats, which have been used in research and are of great importance

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CHAPTER 73

REAGENTS, SOLUTIONS, STAINS, AND CULTURE MEDIA USED IN PARASITOLOGIC AND TROPICAL MEDICAL PROCEDURES

ALFONSO BONILLA NAAR

A

Alcohols.—

Absolute Alcohol.—

Absolute alcohol is water free alcohol. Squibb alcohol is 99.8 per cent. The following method is recommended.

Heat crystals of copper sulfate until they lose their water of crystallization and reduce to a white powder by grinding in a mortar. Heat in an evaporating dish until the copper sulfate turns white.

Add in small quantities to the 95 per cent alcohol. The water in the alcohol is absorbed by the salt and turns it a bluish color. Copper sulfate should be added until no more change in color takes place which indicates that all the water has been absorbed from the alcohol by the salt.

Filter the alcohol into a dry bottle, stopper tightly and seal with petroleum jelly to protect from moisture of the air.

Ethyl Alcohol.—

Prepared in various strengths from 95% alcohol. Pour 95% alcohol into a graduated buret up to the mark desired for the percentage of alcohol to be prepared. Add distilled water up to the 95 mark.

Example. To prepare 40% alcohol, pour 95% alcohol into a buret to the mark 40; add distilled water to the mark 95, mix, let the air bubbles volatilize off, and dilute to 95 c.c. with distilled water.

Methyl Alcohol.—

Methyl alcohol should be acetone free. We recommend that made by the National Aniline Company, New York.

Alkaline Bath.—

Before staining old smears of malarial parasites. Use for several hours.

Alum Carmine.—

Alum carmine is used like cochineal alum to stain taenias, trematodes, etc. It stains the calcareous structures deeply.

Powdered carmine	1 Gm.
2.5% aqueous solution of ammonium alum	100 c.c.

Boil for 20 minutes. Filter when cool.

Alum, Cochineal.—

This does not overstain. It is recommended by Guyer for the Platyhelminthes a helminths and embryos.

Potassium alum	6 Gm.
Powdered cochineal	6 Gm.
Distilled water	90 c.c.

Boil for half an hour Decant the supernatant fluid after it has boiled Add more water and boil until it is evaporated to a volume of approximately 90 c c Filter when cool, and add a crystal of thymol or of salicylic acid to prevent development of molds If the worm is pigmented, treat with chlorine or hydrogen peroxide vapors before staining

Amann's Solution—

This is a clarifying fluid for helminths

Crystallized phenol	1 Gm
Lactic acid	1 Gm
Glycerin	2 Gm
Distilled water	1 c c

Apathy's Cement (Peacock) —

Canada balsam	1 part
Liquid paraffin	1 part

Heat in porcelain receptacle until no further vapors of turpentine are given off and the mixture becomes a golden yellow color. Before applying, heat the mixture Apply with a spatula

Azur II Eosin (For staining microfilariae) —See Feng's Azur II Eosin

B

Balsam, Canada.—See Canada Balsam

Barret and Yarbrough Medium (For cultivation of *Balantidium coli*) —

Inactivated human serum	1 part
0 5% solution of sodium chloride	16 parts

Sterilize by filtration, and distribute in 8 c c quantities in test tubes

By means of a pipette, inoculate the tubes with 0 1 c c of stool specimen and incubate at *37° C (98 6° F)*

Transplant every 24 to 48 hours

The greatest number of parasites will be found in the bottom of the culture, and cysts may appear

Basnuevo Solution (For preservation of helminth eggs) —

Formalin	15 c c
Glycerin	20 c c
Water	100 c c

Add 25 c c of this solution to about 100 grams of fecal material (1 part of the solution for 4 parts of fecal material)

Bass and Johns' Medium (1912) (For cultivation of human plasmodium) —

This medium is used to obtain one generation only

Sterilize 50% dextrose solution on 3 consecutive days at 100° C

Place 0 1 c c in a defibrination flask

Make venipuncture, withdraw 10 c c of blood, and place in a defibrination flask If 20 c c of blood are to be used, use 0 2 c c of dextrose solution Do not expose the blood to the air for too long a period of time

Defibrinate by stirring gently with a stirring rod, and take care to prevent formation of air bubbles The stirring rod can be passed through the cork or cotton stopper.

The height of the blood column in the culture tubes should be 2 5 to 5 cm This will give a serum column of approximately *1 25 to 2 5 cm* *More than 2 5 cm* or less than 1 25 cm is not advisable, since the parasites will die before undergoing segmentation

The parasites live and reproduce in the blood below the serum level, in not more than 0 1 c c They can be removed with a capillary pipette Take care not to contaminate the cultures

To Cultivate Several Generations To obtain more than one generation (up to 3), the authors recommend the method free of leucocytes by centrifuging to force the leucocytes up to the surface of the erythrocytic column

Remove the serum and place in the culture tubes

Pass a capillary pipette through the layer of leucocytes and take from the central part of the red cell column the blood necessary for the culture

For subcultures transfer the infected blood into fresh blood together with its serum using 10 times as much infected blood as fresh blood Transplants should be made every 48 hours after segmentation The optimum temperature is 39° C (102 2° F)

Belesse s Fluid (Peacock) (For mounting Anopheles larvae) —

Chloral hydrate	160 Gm
Gum arabic	15 Gm
Syrup of glucose	10 c c
Acetic acid	5 c c
Distilled water	20 c c

The Division of Malariology of Venezuela (Cova Garcia) uses the following formula

Chloral hydrate	100 Gm
Powdered gum arabic	60 Gm
Glycerin	40 c c
Distilled water	100 c c

Bland Goldstein Wenrich and Weimer Medium (For cultivation of *Trichomonas vaginalis*) —

This medium is composed of nutrient agar slants covered with a modified Ringer solution to which 0 25 Gm of desiccated Loeffler serum medium is added for each 100 c c of solution

Agar —

Use dehydrated Difco Bacto nutrient agar (extract of beef, peptone and agar)

Place 23 Gm of Bacto nutrient agar in 1 000 c c of cool distilled water

Boil in a water bath for 20 minutes until completely dissolved Filter through a double layer of cotton which has been soaked in hot water If the filtrate is not clear repeat until clear

Distribute in test tubes in 5 c c quantities

Sterilize in an autoclave at 15 pounds pressure for 20 minutes and slant

Allow to cool and cover the surface of the slants with modified Ringer solution (alkaline and add 0 25 Gm desiccated Loeffler serum Difco for each 100 c c

Modified Ringer Solution.—

Sodium chloride	6 Gm
Potassium chloride	0 10 Gm
Sodium bicarbonate	0 10 Gm
Calcium chloride	0 10 Gm
Distilled water	1 000 c c

Bles Fixative (To fix insects for sectioning) —

This solution can be injected into the segments of the insect It is recommended by Craig and Faust (1943a)

Boeck and Drbohlav Medium (For cultivation of amebae, especially *Endamoeba histolytica*) —

Locke's Solution (Modified).—

Distilled water	1,000 c c
Sodium chloride	9 0 Gm
Calcium chloride	0 2 Gm
Potassium chloride	0 4 Gm
Sodium bicarbonate	0 2 Gm
Glucose	2 5 Gm

Sterilize in an autoclave at 15 pounds pressure for 30 minutes

Locke Egg Serum Medium (L.E S) —

Mix the whites and yolks of 4 eggs thoroughly

Add 50 c c Locke solution

Mix and filter through gauze

Place in 5 c c quantities in 15 c c vials Slant in an autoclave and sterilize at 15 to 20 pounds pressure for 30 minutes

Preparation of the Blood Serum.—

Inactivate the serum in a water bath at 56° C for ½ hour

Preparation of the Medium for Inoculation.—

Dilute the blood serum so that the final concentration of serum and Locke solution is 1 part serum to 8 parts Locke solution

Cover the tubes with this mixture to a depth of 1 cm above the slant Incubate for sterility before using

Locke Egg Albumin Medium (L.E A.) —

Make a 1% solution of crystallized egg albumin in Locke solution and sterilize by filtration Add to the culture tubes containing the egg slants as described above Incubate at 37° C

Before inoculation, add one loopful of rice starch

Bonacci Medium (1934) (Numbers 1, 4, and 9) (For cultivation of *Trypanosoma cruzi*) —

Medium No 1.—

Witte peptone	3 Gm
Sodium chloride	1 Gm
Agar	2 Gm
Nutrient beef broth	200 c c

Dissolve the ingredients in the hot nutrient broth and neutralize Place in an autoclave at 115° C for 20 minutes

Filter through cotton, distribute in 100 c c quantities in Erlenmeyer flasks, and sterilize at 110° C (200° F) for 20 minutes

Store in an ice chest until ready for use

Liquefy and cool to 40° C

To each 100 c c , add 0 5 Gm glucose and 5 c c young guinea pig blood

Media No 4 and No 9 —

These are similar to Medium No 1 except for the amount of peptone and sodium chloride Medium No 4 contains 2 5 Gm peptone and 0 7 Gm sodium chloride Medium No 9 contains 3 Gm peptone and 0 7 Gm sodium chloride to each 100 c c of the agar mixture

Bonilla-Naar Congo Red Method.—

This is used to stain larvae of helminths and trematodes and proglottids of teniae See Congo red solution

Borax Carmine (Grenacher) —

Borax 4% aqueous	100 c c
Carm ne	1 Gm

Immediately add 100 c c of 70% alcohol Filter after 24 hours Allow the tissue to rema n in the solution for 24 hours to several days Without washing place it in acid alcohol until not much stain comes out (cloud)

Wash and harden in neutral al ohol (Guyer)

Bouin Fixative —See Chapter 69

Boye s Stain (For human hematozoa especially in the thick drop) —

Use Stevenel stain Craig notes that he has not used this stain but recommends it as a good subst tute for Romanowsky or its derivatives

Brilliant Cresyl Blue —See Chapter 68

Brutsaert and Henrard Medium (1938) (For *Trypanosoma gambiense* and *T rhodesiense*) —

R nger s solution conta ning 0 6 per cent sod um chloride and Tyrode solution are used (see Tyrode solut on)

Sterilize by filtration and distribute in test tubes using 2 c c of Ringer s solution for 2 5 c c of Tyrode solution

Add to each tube 2 c c citrated human blood (1% citrate) and incubate to determine sterility (24 hours at 3 ° C

Store in a refrigerator The med um must be used within 2 weeks of making

The blood is collected in a sterile syringe containing 1 c c of Roche s Liquoid, 0 5 c c for each 10 c c of culture medium

Incubate at 25° to °8° C The culture requires 10 to 12 days for growth

C

Cable Modification.—See Gastric Juice Artific al

Canada Balsam (in xylol or benzol) —

Canada balsam can be procured ready for use or it may be made as follows

Heat the res n until it becomes fragile or brittle when allowed to cool

Dissolve in xylol until a fairly thin solut on is obtained

Add a small p ece of marble to prevent acidification and discoloration

The desired consistency can be obta ned after filtrat on by evaporating over a small flame

Carmine Acid.—

Glacial acetic a id	45 c c
Distilled water	55 c c
Carmine powder in excess	

D ssolve the carmine in the acetic acid

Heat without bo ling cool and filter

Carnoy s Liquid (Fixative) (Peacock) —

Ethyl alcohol	75 c c
Glacial acet c acid	25 c c

Carnoy s Liquid (Fixative) (Justin Andrews) —

Glacial acetic acid	10 c c.
Absolute alcohol	60 c c
Chloroform	30 c c

Cedar Oil.—

Cedar oil is usually purchased ready for use Specify whether it is to be used to clarify t ssue or for oil immersion purposes

Cleveland and Collier Medium (For cultivation of *E histolytica*) —

Distilled water	1,000 c c
Difco liver infusion agar	30 Gm
Na_2HPO_4	3 Gm

Sterilize in a slanting position in an autoclave and allow to solidify in that position Cover the surfaces with a mixture of 1 part of fresh horse serum and 6 parts of 0 8 per cent sodium chloride solution which has been previously filtered The reaction need not be adjusted

Before inoculating with amebae, add a small amount of sterile rice starch to each tube

Congo Red Solution (Bonilla Naar) —

This is used to stain larvae of Trichinellae, Ancylostomidae, and trematodes and proglottids of Taenia

Saturated alcoholic solution of Congo red	1 part
Distilled water	1 part

To Stain Proglottids —

Without preliminary fixation, and using a very fine needle, inject the recently expelled proglottids in the excretory orifice, or in the highest zone opposite this pore

For staining the entire mature segments, the segment or even 2 segments are placed between slides and compressed by 2 elastic bands

Place the slides in Schaudinn fixative to which 20% acetic acid has been added, for 24 hours

Wash thoroughly with water

Place in iodized alcohol for 10 minutes

Place the slides in the stain and control microscopically every 15 minutes

Place in alcohols of increasing strength, then in absolute alcohol, 2 hours in each

Finally, place in methyl salicylate for a few seconds

Mount in neutral Canada balsam

Staining of Larvae (A caninum, A. duodenale, N americanus, T spiralis) —

This method is very simple The larvae undergo little or no deformity

For larvae of Ancylostomidae and Trichinellae, artificially digested (see gastric juice), place them in a tube containing warm 30% alcohol to which a few drops of the Congo red solution have been added Control under the microscope If necessary, add a few more drops of Congo red solution When they are properly stained, place in alcohols of increasing strengths, and finally in absolute alcohol Leave in each alcohol for ½ to 1 hour to dehydrate slowly and so prevent shrinkage of the larvae

Finally place for 3 minutes in methyl salicylate Using a pipette or a capillary dropper, remove the alcohol

Mount the larvae in a drop of balsam

D

D'Antoni's Standardized Iodine Stain (For staining cysts of protozoa and eggs of helminths, and for preserving fecal specimens in transit) —

Weigh 100 Gm of potassium iodide (Merck or Baker) and place in a chemically clean 1,000 c c volumetric flask

Add distilled water to the 1,000 c c mark.

Weigh to the fourth decimal place a 25 c c clean and dry volumetric flask and record the weight

Fill the flask to the mark with the potassium iodide solution (above) and again weigh to the fourth decimal place

Subtract the weight of the empty flask from that of the flask plus solution to determine the weight of 25 c c of the 10% potassium iodide solution This weight should theoretically be 26 925 Gm, but due to the deliquescence of KI, the actual weight of the

solution will be less than the theoretical weight Divide the actual weight by the theoretical weight and subtract the quotient in terms of percentage, from 10 the desired percentage to determine the actual percentage of the solution Thus 100 actual percentage x 10% x = Gm of potassium iodide

Subtract 100 from the number of grams represented by x to obtain the number of grams of KI to add to the original 1 000 c c of solution to obtain a standardized 10% KI solution

Staining Solution —

Add 1 5 Gm powdered iodine crystals to each 100 c c of standardized 10 per cent KI solution Allow to stand for 4 days before use Filter before use Do not allow to remain unstoppered

The stock solution keeps for long periods without deterioration if kept tightly stoppered

Decalcifying Solution.—

Nitric acid concentrated	10 c c
70% alcohol	90 c c

Dobell Method (1928) (For producing cysts in cultures of amebae) —

If rice starch is added to cultures to which no rice starch has previously been added *many cysts will appear*

Dobell Laidlaw Media (For cultivation of *E histolytica*) —

Medium No 1 —

This is similar to the Boeck and Drbohlav medium except that a modified Ringer solution is used in place of the Locke solution

NaCl	9 Gm
$CaCl_2$	0 2 Gm
KCl	0 2 Gm
Water	1 000 c c

Medium No 2 —

Undiluted sterile horse serum is used in place of egg and Ringer solutions

Place the serum in tubes slant and inspissate at 80° C for not more than 1 hour and 10 minutes

Cool and incubate at 37° C for 48 hours to determine sterility

Cover the slants with egg albumin solution or the solution described as Medium No 1

Add rice starch at the time of inoculation

The reaction need not be adjusted

Donaldson Lugol Eosin Solution (Modified by Sumerlin 1934) (For staining cysts of protozoa) —

Saturated solution of eosin in physiologic saline	1 part
Saturated solution of iodine in physiologic saline	1 part
Physiologic saline solution	2 parts

Keep in separate bottles

Duboscq Brasil Solution (Rapidly penetrating fixative) —

80% alcohol	150 c c
Picric acid	1 Gm
Before using add	
40% formalin	60 c c
Acetic acid	15 c c

E

Egg Albumin Fixative (For fixing protozoa, etc , to slides) —

Egg white	50 c c
Glycerin	50 c c
Sodium salicylate	1 Gm

Beat the egg white and glycerin and remove the foam

A crystal of thymol may be used instead of the salicylate as a préservative if desired

Errecart Solution (1941) (To dehemoglobinize thick drops of blood) —

40% formalin	1 c c
Acetic acid	0 2 c c
Physiologic saline	100 c c

F

Faust Zinc Sulfate Solution (For flotation of cysts, eggs, and larvae of helminths) —See Chapter 71

Feng Azur II Eosin (For staining microfilariae) —

To 500 c c of physiologic saline, add 1 c c of 1% azur II and 0 1 per cent sodium carbonate solution This is the stock

For use, add 4 c c of the azur II stock solution to 96 c c of saline

The eosin solution used in Feng's stain is made by dissolving 1 Gm of eosin in 4,000 c c of saline

Feng Hemalum Stain (For staining microfilariae) —

Dehemoglobinize the blood films in saline

Place the slides in warm 70% alcohol for 15 minutes

Pass through tap water, then slightly alkaline water

Transfer to staining jar containing hemalum and stain for 3 to 5 hours

Decolorize in 70% alcohol containing 1% hydrochloric acid until properly differentiated

Wash in tap water

Dehydrate in increasing strengths of alcohol, then absolute alcohol

Clarify in xylol 5 minutes

Mount in balsam

Feng's Methyl Green Pyronin (For staining microfilariae) —

Add 0 2 Gm of methyl green

and 0 075 Gm of pyronin

to 100 c c of physiologic saline

Dehemoglobinize blood films in physiologic saline

Stain for 12 to 36 hours in Feng methyl green pyronin stain

Dehydrate rapidly in increasing strengths of alcohol (70, 85, 95%), then in absolute alcohol

Clear in xylol and mount in balsam

Field Stain (1941) (Rapid stain for thick drops of blood) —See Chapter 68

Formalin (Formol) —

Commercial formalin is a saturated aqueous solution of formaldehyde gas and contains approximately 40% of formaldehyde by weight This solution is spoken of as 100% solution of formalin and is diluted when determined concentration of formalin and not formaldehyde are desired (Cable) See also Chapters 69 and 70.

Formalin Acetic Acid (For dehemoglobinizing thick drops or smears of blood) —

Formalin	5 c c
Acetic acid	1 c c
Distilled water	100 c c

Formol Sublimate Solution (Recommended by Pearl Raymond as an extremely satisfactory means of killing and fixing protozoa) —

Add mercuric chloride to 10% formalin until saturation is reached

The tissue or other material can be washed in water or in a 4% formalin solution After passing the material through alcohols of increasing strengths, the material can be preserved in this formalin or in a 70% alcohol solution

Foure s Chloral Gum (For mounting and studying the Trombid idae larvae) (Boshell Manrique and Kerr) —

Distilled water	50 c c
Chloral	50 Gm
Glycerin	20 c c
Gum arabic	30 Gm

Filter

This procedure does not ensure long preservation of the specimen

G

Gage Stain (For hypopygium of mosquitoes) —

Acid fuchsin	0 5 Gm.
10% HCl solution	25 c c.
Distilled water	300 c c

Place in 10% potassium hydroxide solution the genitalia which are adherent to the abdominal segment

Place in a water bath for 20 minutes

Transfer to hot distilled water for ¼ to ½ hour or to cold water for 12 hours.

Place the genital a in the stain for 3 hours

Decolorize in phenol 5 minutes

D ssect in the same phenol and mount in Canada balsam

Gastric Juice Artificial (For digestion of *Trichinella spiralis* in muscle) —

This is a pepsin solution in hydrochloric acid Although the quantities vary accord ing to different authors a solution of 0 6% pepsin in 0 3% to 0 4% hydrochloric acid is excellent for digestion of muscle tissue and the capsules of the larvae which are freed from the tissue

After d gestion, they are then passed to the Baermann apparatus and are isolated by thermotropism

Cable Modification.—

Hydrochloric acid concentrated	7 to 10 c c
1 10 000 peps n	6 Gm
Distilled water to make	1 000 c c

Geiman s Medium (Modified by Groot and Hernández) (For cultivation of *T cru i*) —

The original medium is used in the cultivat on of *Bartonella bacilliformis*

Bacto agar	20 Gm
Proteose peptone No. 3	20 Gm
NaCl	5 Gm.
Distilled water	1 000 c c

D ssolve and adjust the reaction to pH 7 6 to 7 8

Sterilize in the autoclave

To 75 c c of this medium, liquefied and cooled to 45° C., add 25 c c *of fresh rabbit* blood and 0 2 c c of the following mixture *sterilized by filtration*

Ascorbic acid	10 mg
Glutathion	40 mg
Ringer's solution	20 c c

Groot Hernández Modification.—

Add to the water of condensation of the tubes 2 to 5 c c, according to size, of the following solution, previously sterilized

Bacto peptone	12 5 Gm.
NaCl	2 5 Gm
Bacto beef dehydrated	25 0 Gm.
Glucose	2 5 Gm
Distilled water	750 c c

This is the same solution as that added to the Kelser medium *for T. cruzi* with such good results

The glutathion stabilizes and protects the vitamin C against oxidation The mixture of glutathion and vitamin C must not be more than 10 days old

Giemsa Stain—See Chapter 68

Glycerine Jelly.—

Place 6 Gm of granulated gelatin in 40 c c of distilled water and allow to soak for 15 minutes

Liquefy in a water bath at a temperature not to exceed 75° C

Filter several times through a porous cloth or gauze which has been soaked in hot water

Dissolve 1 Gm. of phenol in 50 c c of glycerin and add the gelatin

Gram Stain—

The Gram stain is recommended by Kouri for staining Protozoa, in addition to its well known use in bacteriology There are a number of modifications For details, see Gradwohl (1948)

Gray and Tulloch's Medium (1907) (For cultivation of *T gambiense*) —

This is NNN medium using dog instead of rabbit blood

Gum Chloral (Foure) (For mounting Trombidiidae) —See Foure's Gum Chloral

Gum Damar in Xylol (For permanent mounts) —

Make a saturated solution of gum damar in neutral xylol by placing the mixture of gum and xylol in an incubator and shaking a number of times a day until it is of a heavy syrupy consistency Filter through 4 layers of gauze and store in a brown bottle Allow to sediment completely, then decant the supernatant fluid

Gum, 5% Formolized *(For preservation of mosquito eggs)* —

Powdered gum arabic	60 Gm
5% formalin	10 c c

H

Heidenhain Hematoxylin.—See Hematoxylin

Helminth Eggs and Larvae —*See* Chapter 72

Hemalum Stain —See Feng's Hemalum Stain

Hematoxylin, Harris —See Chapter 70

Hematoxylin, Heidenhain, Iron—

0.5 and 1 per cent solutions of iron hematoxylin are prepared from a 10% alcoholic stock solution, which should be oxidized

Iron hematoxylin	5 Gm
95% ethyl alcohol	50 c c

To make a 0.5% solution, multiply any quantity of the stock solution by 19 to determine the quantity of distilled water to be added to it. Thus if 10 c c of the 10% stock solution are used, add 190 c c of distilled water.

To make a 1% solution, multiply any quantity of the stock solution by 9 to find the amount of distilled water needed. Thus for 10 c c of the stock solution, use 90 c c of distilled water.

Hematoxylin Johnson—See Johnson Hematoxylin

Hematoxylin, Mallory—See Mallory Hematoxylin

Hogue's Medium—

No 1 (For cultivation of Trichomonas)—

Locke solution	200 c c
Hen's egg	1

Break the egg into a container with glass beads, add the Locke solution, and mix well.

Place in a water bath for 15 minutes, stirring constantly.

Filter through cotton with the aid of a suction pump.

Distribute in 6 c c quantities in test tubes.

Sterilize in an autoclave for 20 minutes at 15 pounds pressure.

No 2 (For cultivation of intestinal flagellates)—

Sodium chloride, 0.7% solution, 600 c c

Whites of 6 eggs. Place egg whites in a glass flask containing glass beads and mix vigorously.

Add the saline solution and place in a water bath for 30 minutes. Filter through cotton using suction.

Distribute in 5 c c quantities in test tubes.

Place in an autoclave for 20 minutes at 15 pounds pressure.

Incubate at 36° C. Subculture every 24 hours.

The flagellates are more numerous on the surface of the medium.

I

Iodine, D'Antoni—See D'Antoni's Iodine

Iodine Solution (For staining cysts of protozoa and eggs of helminths)—

Crystalline iodine	5 Gm
Potassium iodide	10 Gm
Distilled water	100 c c

Dissolve the potassium iodide in distilled water in a clean flask. Add the iodine crystals a small amount at a time, mixing until the crystals are completely dissolved. Filter and keep well stoppered. Use in dropping bottles. Store in the dark. Prepare fresh solution each 20 days to one month.

Iron Hematoxylin—See Hematoxylin Heidenhain, Iron, and John's Hematoxylin

J

Jameson Medium (For cultivation of *Balantidium coli*)—

Use the Dobell and Laidlaw medium. Subculture every 48 hours or every 3 to 5 days. The pH must not be allowed to drop below 5.0, the optimum being 5.4 to 8.0. Elements in conjunction are observed, but no cysts.

Janer Solution (For staining nucleus, karyosome, and chromatin, particularly in the pre cystic forms of amebae) —

This is a 2% solution of copper sulfate According to Talice, the peripheral chromatin band in the nucleus and the karyosome appear more outstanding and thicker than in preparations stained with iron hematoxylin

Jenner Stain —

(Jenner's stain is used like Leishman and Wright stains, especially for Leishmania.)

Mix equal parts of 1 2% aqueous water soluble eosin and 1% aqueous medicinal *methylene blue (certified)*

After thorough mixing, allow to stand at room temperature for 24 hours

A precipitate with a metallic sheen will form

Collect the precipitate on a filter paper and wash several times with distilled water, until the water which comes through the filter paper is almost colorless

Allow the washed precipitate to dry

Place the dried precipitate in a bottle and stopper tightly Keep in a dark place

Dissolve 0 5 Gm of the precipitate in 100 c c of pure methyl alcohol (National Aniline)

Place this stain, without diluting, on the smear and allow to remain 1 to 2 minutes

Add a few drops of distilled water until a metallic sheen appears and allow to stain for 5 to 15 minutes or more, according to the depth of stain desired

Johnson Iron Hematoxylin Method (For staining protozoa) —

Fix in warm Schaudinn fixative for 10 to 20 minutes

Place in 95% alcohol to which a few crystals of iodine have been added, for 1 to 3 minutes. This removes the mercuric chloride

Immerse in 75% alcohol for 5 minutes or more The slides can be left in this alco hol for several days without harm

Wash gently in running tap water or in a large receptacle

Place in an aqueous 0 5% hematoxylin solution (10 c c of the 10% stock solution in 95% alcohol, plus 190 c c of distilled water) for 10 minutes The stock solution should be ripened by age, or it will not stain The solution should be prepared in advance For rapid ripening we recommend ultraviolet rays, oxygenated water, or mercuric oxide (see Harris mondification)

Differentiate by decolorizing for 6 to 10 minutes in 0 25% iron alum, controlling microscopically in the usual manner Calculate the time as follows (not recommended) amebae, 12 minutes, flagellates, 5 to 10 minutes, keeping in mind the size of the protozoa and the thickness of the preparation

Wash in running tap water

Dehydrate in alcohols of increasing concentration

Clarify in xylol or toluol and mount in neutral balsam

NOTE When staining *Balantidium coli*, use Heidenhain's method The prepara tion must not dry between the steps

J S B Stain (Jasivant, Singh, and Bhattacharji) (For blood parasites—Plasmodium, Leishmania, and Trypanosoma) —

(a)	Medicinal methylene blue	0 5 Gm
	Potassium chromate	0 5 Gm.
	Sulfuric acid, 1% solution	3 0 c c
	Distilled water	500 c c
(b)	Eosin, water soluble	1 Gm.
	Distilled water	500 c c

K

Kahle Liquid Fixative (For arthropods especially larvae of insects) —

Commercial formalin	6 parts
95% ethyl alcohol	15 parts
Glacial acetic acid	1 part
Distilled water	30 parts

Keep the tissue in the fixative for 12 to 24 hours

Pass through 50% and 70% alcohols then place in 85% alcohol and keep in this last alcohol

The fixative may be used warm The larvae may be injected with the fixative or cut in slices to allow for better penetration

Kelser Medium (For cultivation of Trypanosoma) —

Bacto peptone (Difco)	12 5 Gm
NaCl	3 5 Gm
Bacto agar granulated	5 0 Gm
Bacto beef dehydrated	25 0 Gm
Distilled water	500 0 c c

Add the agar to the distilled water and place in a water bath at 55° C for 1 hour

Add the peptone and sodium chloride

Maintain at boiling for 5 minutes stirring constantly

Filter through cotton until clear

Neutralize with N/1 sodium hydroxide

Add the dehydrated beef to the mixture while still hot

Mix well and distribute in 5 c c quantities in test tubes or in 10 c c quantities in flasks

Sterilize in an autoclave at 12 pounds pressure for ½ hour

Cool and solidify

To use dissolve and add 0 25 c c of 1% dextrose solution and 0 5 c c of fresh defibrinated guinea pig blood to each tube

If the quantity of water of condensation in the tubes is small add 1% dextrose solution to which have been added 2 parts of a peptone similar to that used in the medium

In using the culture flask add 2 c c of 1% dextrose solution taking care not to exceed this quantity

Numerous trypanosomes will be observed on the third or fourth day Leishmanial forms will be observed first

Kligler Medium (For cultivation of *Leishmania*) —

1% dextrose agar	10 parts
0 85% saline solution	90 parts

Sterilize in an autoclave Final pH should be 7 0 to 7 6

Distribute in 5 to 10 c c quantities

Cool to 48° to 50° C

Add to each tube 1 part of fresh sterile rabbit blood for 10 parts of medium and slant in an icebox

Test for sterility by placing in an incubator at 37° C for 24 hours

Knowles and Das Gupta Method (For examination of *L donovani* in the thick drop) —

Place 4 drops of blood in the center of a slide and spread in a ¼ inch square using a needle

Allow to dry at 37° C in a Petri dish for 2 hours.

Immerse for 5 to 10 minutes in a mixture of 4 parts of 2% acetic acid and 1 part of crystalline tartaric acid

Dry fix in methyl alcohol and stain

Kofoid and Swezy Medium (For the cultivation of *Trichomonas hominis*) —

Locke solution	9 parts
Rabbit or guinea pig serum	1 part

Sterilize the Locke solution in an autoclave

Inactivate the serum for ½ hour at 56° C

Mix the Locke solution and the serum thoroughly and filter through a Berkefeld filter Distribute in 5 c c quantities in test tubes and incubate at 37° C

Kopel Giemsa Stain Modification (For malarial parasites) —

Fix thin films in absolute ethyl alcohol in Koplin jars for 15 seconds, dry, and place in a horizontal position on a staining rack

Flood with diluted Giemsa stain and stain for ½ hour

Wash with buffer solution pH 6 4 Allow to dry in a vertical position

To prepare modified Giemsa stain, dissolve 0 5 Gm of Giemsa powder in 33 c c of glycerin Let stand for 2 hours at 60° C, shaking at ½ hour intervals

Add 33 c c of 100% ethyl alcohol and shake thoroughly

Add 1 c c of this stock solution to 24 c c of buffer solution pH 6 4

L

Langeron Lacto Phenol —

Glycerin	2 parts
Distilled water	1 part
Phenol crystals	1 part
Lactic acid	1 part

L E A and L E S Medium (For culture of *E histolytica*) —See Boeck and Drbohlav

Leishman Stain.—

The preparation given here is that cited by Craig

Prepare a 1% solution of medicinal methylene blue in distilled water rendered alkaline by the addition of 0 5% sodium carbonate

Heat for 12 hours at 65° C in the dry heat oven and allow to remain at room temperature for 10 days

Prepare a 1 1,000 solution of eosin (certified)

Mix equal parts of the methylene blue solution and the eosin solution in a wide mouthed container Allow to stand for 6 to 12 hours, mixing at intervals

Collect the precipitate by filtration through a small filter paper and wash with distilled water until the water which comes off is but slightly blue The precipitate may be removed from the filter paper with a spatula and allowed to dry in an oven, or the filter paper, with the precipitate, may be placed in an oven The dry precipitate is placed in a dark bottle and kept well stoppered The stain is prepared from this precipitate

Dissolve 0 15 Gm of the dry powder in 100 c c of methyl alcohol (National Aniline)

Method of Staining —

Do not fix, since the stain contains sufficient alcohol to act as fixative

Cover the smear with the stain for 1 to 3 minutes, counting the number of drops used To prevent evaporation of the stain, cover with a bell jar (this is optional)

After 1 to 3 minutes, or longer if a more intense stain is desired, add to the preparation, *without losing any stain*, the same number of drops of neutral distilled water as were used for the staining The stain now acts by ionization

We use 3 minutes for the stain and 8 minutes for the mixture of stain and water, some prefer 1 and 4 minutes, respectively

Wash with tap water, dry, and observe microscopically

Locke Solution —

Sodium chloride	9 Gm
Sodium bicarbonate	0 2 Gm
Potassium chloride	0 42 Gm
Calcium chloride	0 25 Gm
Glucose (may be omitted)	2 5 Gm
D stilled water	1 000 c c

NOTE Andrews uses potass um bicarbonate instead of the sodium bicarbonate and 0 24 Gm of $CaCl_2$ instead of 0 25 Gm

To prevent precipitat on of the calcium carbonate d ssolve the calcium chloride separately in a small amount of water and add to the rest of the solution (Cable)

Locke Solution (Modified by Young and Van Sant).—

Sod um chlor de	9 Gm
Potassium chloride	0 4 Gm
Calc um chloride	0 2 Gm
Sod um c trate	10 0 Gm
D st lled water	10 0 c c

This solut on is used in the diagnos s of *L donovani* by centrifugalizat on of blood Dilute 5 c c of blood in Locke solut on and centr fuge at 750 r p m

Longley Clausen and Tatum Method (For cultivation of trypanosomes in chick embryo) —

Fertile chicken eggs are incubated for 8 to 10 days at 39° C
Inject 0 2 c c quantities for each egg into the allantoic cavity
The embryo will d e on or abo t the fourth or fifth day
Sub culture on the fifth day

Lugol Solution (For stain ng eggs and cysts of paras tes) —

Iod ne resubl med	5 Gm
Potassium iod de	10 Gm
D st lled water	100 c c

Rub up the iod ne in the potass um iod de and add the water a small amount at a time grind ng the iodine in the water until all the water has been added

Filter after 24 hours

Lynch Medium (For cult vat on of *Tr homonas vag alis*) —

0 5% sod um chloride solution	10 parts
Human blood serum	1 part

Sterilize the sod um chloride sol tion in an autoclave and the ser m by filtration through a bacteriolog c filter

M x the substances in the proportion given in the formula and pass through a bacterial filter

D stribute n 5 c c quantit es n test tubes

Inc bate at 37° C

M

MacCallum Macerating Liquid —

Nitr c a i l	1 part
Glycerin	2 parts
Water	2 parts

MacGregor Liquid (For preserving stomachs and salivary glands of mosquitoes) —
This formula is recommended by M A Barber —

5% borax solution	10 c c
40% formaldehyde solution	10 c c
Glycerin	0 25 c c
Water to make	100 c c

Mallory Phosphotungstic Acid Hematoxylin.—

Hematein (ammonium)	0 1 Gm
Water	100 c.c
Phosphotungstic acid	2 0 Gm

Dissolve the hematein in a small quantity of hot water

Cool and add the rest of the mixture

If the stain is weak, allow it to ripen for 2 to 3 weeks, and add 5 c.c of 0 25% aqueous potassium permanganate solution

Hematoxylin may be used in place of the hematein ammonium, if 10 c c of the aqueous potassium permanganate are added for ripening

Histologic sections are kept in the solution 2 to 24 hours This is a special stain for chromosomes and mitotic elements

Mann Stain (For staining details of the structure of Rhizopoda and Mastigophora, and museum material) —

1% aqueous solution of methylene blue	35 c c
1% aqueous solution of eosin	45 c c
Distilled water	*100 c c.*

Technic.—

Fix in Schaudinn fixative

Pass through 50% then 70% alcohol containing a few iodine crystals, enough to give a port wine color

Place for 10 minutes each in 80%, then 90% alcohol

Place in distilled water for 10 minutes

Place in Mann stain for 4 to 12 hours, controlling the stain under the microscope

Wash thoroughly in distilled water

Differentiate in 70% alcohol to which orange G has been added (a few drops of a saturated solution in 100 c c of 70% alcohol)

Wash in distilled water

Place for at least 5 minutes each in 30%, 50%, 70%, and 90% alcohol

Place in absolute alcohol for 10 to 15 minutes

Place in equal parts of absolute alcohol and xylol for 5 minutes

Clear in xylol

Mount in neutral balsam

NOTE As with the hematoxylin method, do not allow the preparation to dry during any of the staining steps

Mayer "Hemalum" Method (For Rhizopoda and Mastigophora) —See Chapter 69

Mayer "Hemalum" (Hematein Alum) (Used in the de Feulgen Technic, Cowdry, 1928) —

Hematein	1 Gm
90% ethyl alcohol	50 c c
Alum	50 Gm
Distilled water	1,000 c c

Dissolve the hematein in the alcohol with heat and add the water in which the alum has been dissolved Add a crystal of thymol or salicylic acid

Mayer Paracarmin.—

Acid carmine	1 Gm
Aluminum chloride	0 5 Gm
Calcium chloride	4 Gm
70% alcohol	100 c c

Mercurochrome 1% Aqueous Solution (For staining chitin especially hypopygium) (Osorno Mesa) —

Preparations stained by this method have remained in excellent condition to date (10 years)

Methyl Green Pyronin —See Feng s Methyl Green Pyronin

Murrayite (Murray cement) —

Murrayite is used to seal museum jars or flasks *

N

Noguchi Lindenberg Medium (For cultivation of Leishmania) —

This is one of the best methods for cultures of Leishmania Leptospira and Herpetomonas

0 9% sodium chloride solution	800 parts
Fresh rabbit serum	100 parts
2% nutrient agar pH 7 2	100 parts
Rabbit hemoglobin 1 part defibrinated blood in 3 parts of distilled water	10 to 20 parts

Leishmania grow on the surface and at times up to a depth of 4 mm The cultures will show growth on the fourth or fifth day but growth may be delayed for as long as 2 or 3 weeks Best results are obtained at 18° to 20° C but the organisms grow well also at 26° C

This medium can be kept in the refrigerator for 3 months. Subcultures must be made every 3 weeks

Noguchi-Ohira Medium (For cultivation of intestinal flagellates) —

Ascitic fluid	500 c c
Ringer solution	500 c c

Mix and distribute in 5 to 10 c c quantities in test tubes

Add a small piece of guinea pig kidney to each tube The kidney should be sterile

Subcultures should be made each 24 hours if incubated at 37° C and every 48 hours if the temperature of incubation is 22 to 27° C

Noland Stain (For temporary staining of flagellates and ciliates) —

Saturated aqueous solution of phenol	*80 c c*
40% formaldehyde solution	20 c c
Glycerin	4 c c
Gentian violet	20 mg

Moisten the stain with 1 c c of water before adding the other ingredients

Mix one drop of the stain with one drop of the material

Noller Medium (For cultivation of flagellates of plants) —

This is a nutrient agar which contains 1% agar and 1% glucose mixed with an equal part of horse blood

*Murrayite can be obtained from the Arthur H. Thomas Co Philadelphia Pa. U S A.

Novy, MacNeal, and Nicolle Medium (NNN agar) (For cultivation of blood flagellates, especially Leishmania and *T cruzi*) —

Agar	14 Gm.
Sodium chloride	6 Gm.
Distilled water	100 c c.

Distribute in 3 c c quantities in test tubes

Sterilize in an autoclave

To use, liquefy the agar in a water bath and add to each tube 1 c c of sterile defibrinated rabbit blood

Mix well by bimanual rotation of the tubes, and slant at room temperature for 12 hours

Test for sterility by incubating for 24 hours at 37° C

If there is very little or no water of condensation, a small amount of sterile physiologic saline can be added to the medium and the medium incubated at 22° to 25° C

O

Osmic Acid (Tetraoxide of Osmium, OsO_4) (Fixative of parasites in blood smears) —

Osmic acid is very volatile The vapors are used to fix protozoa, especially the amebae and trypanosomes Crystals or aqueous solution, commonly 1 per cent, may be used It is advisable to prevent contamination with any solid organic material, since osmic acid is rapidly reduced in the presence of organic matter. Lee recommends a mixture of 2 per cent osmic acid with 1 per cent aqueous solution of chromic acid

P

Paradichlorobenzene Crystals (For preservation of arthropods in museum boxes) —

A few crystals of paradichlorobenzene are used in small carboard boxes or in small receptacles These are placed in the corners of the boxes containing preparations or museum mountings (insects, arachnids, etc.). The crystals should be replaced by fresh crystals twice yearly Mixed with naphthaline, paradichlorobenzene crystals have procured better results in preservation

Picrocarmine —

Ammonium hydroxide	5 c c
Distilled water	50 c c
Carmine	1 Gm

Dissolve the ingredients and add 50 c c. of saturated aqueous solution of picric acid Expose to the air and light for 2 days, then filter.

A few crystals of picric acid may be added to the decolorizing agent used during the staining process

P.V A. Fixative (Polyvinyl alcohol fixative, for trophozoites of intestinal protozoa) —

Acetic acid, glacial	5 0 c c
Glycerin	1 5 c c
Saturated aqueous solution of mercuric chloride	62 4 c c
Ethyl alcohol, 95%	31 2 c c

Heat to 75° C and add while stirring

Polyvinyl alcohol (P.V A powder, Elvanol 90 25 DuPont) — 5 Gm

Remains unchanged for several months

Potassium Dichromate Solution, Specific Gravity 1 35 (For isolation of eggs of helminths from soil) —

Dissolve 40 Gm of potassium dichromate in enough distilled water to make a total of 100 c c, and test the specific gravity Adjust if necessary

Potassium Hydroxide 10% Solution (To clear insects—exoskeleton) —

This solution is used either cold or hot. The cold solution is applied for 12 to 24 hours, the hot for a few minutes (10 to 20). Wash, dehydrate, clear, and mount in neutral Canada balsam or in Euparol for permanent mounts.

Q

Quensel Stain (For staining live amebae) —

This stain does not stain the cysts but it does stain the nuclear structures, chromatin and karyosome.

Saturated solution of Sudan III in 50% alcohol and saturated solution of methylene blue (official) in distilled water are used to make the stain. Filter each solution.

Mix 20 c c of the Sudan III solution with 30 c c of the methylene blue solution.

Filter and collect the filtrate in a vessel containing 50 c c of 10% cadmium chloride (5 Gm in 50 c c of water).

A colorless precipitate will form in the center of the liquid.

Immediately shake gently and 10 to 15 minutes later repeat the process.

Filter. The precipitate will remain on the filter paper. Place the filter paper containing the precipitate in another filter paper and allow to stand overnight.

Transfer the precipitate to a new filter paper, wash with distilled water (25 to 30 c c) rapidly passing through the filter which contains the precipitate.

Dissolve the precipitate in 250 c c of distilled water. If there are fine crystals of cadmium chloride filter until these disappear.

Use 1 drop of stain for 1 particle of stool specimen.

Observe after 5 to 10 minutes. After 20 to 30 minutes the amebae are overstained.

R

Reichenow Medium (For cultivation of pathogenic trypanosomes) —

This is a mixture of citrated human blood and Ringer solution. Each tube contains 1 c c of Ringer solution and 0.6% of sodium chloride.

Sterilize and add to each tube 1 c c of citrated human blood.

Place in a refrigerator for 2 to 3 days before using.

Inoculate and incubate at 24° C.

Subculture every 2 weeks.

Ringer Solution —

Sodium chloride	8 Gm
Potassium chloride	0.2 Gm
Anhydrous calcium chloride	0.2 Gm
Sodium bicarbonate	0.2 Gm
Dextrose (may be omitted)	1.0 Gm
Distilled water	1,000 c c

Roche Liquoid (For cultivating *T. gambiense* and *T. rhodesiense* in Brutsaert and Henrard Medium) —

This is a 1% polyanethol sodium sulfonate solution.

Roger Medium (For cultivation of *L. donovani*) —

This was the first culture medium used for *L. donovani*.

Add 8 Gm of sodium citrate to each 100 c c of 0.85% sodium chloride solution and mix thoroughly. If the solution is not acid, add a small amount of citric acid.

Distribute in 1 c c quantities and autoclave.

Inoculate with 0.5 to 1.0 c c of peripheral blood or with small quantities of splenic or hepatic pulp or bone marrow.

Row Medium (Saline Solution Hemoglobin) (Special medium for Chilomastix, best for *Trichomonas hominis*) —

Obtain 10 c c of rabbit blood by cardiac puncture and defibrinate with glass beads under sterile precautions

Transfer with a pipette to 100 c c of sterile neutral distilled water, pH 7 0 to 7 1

Add 1 volume of this hemoglobin solution to 2 volumes of 1 2% sterile sodium chloride solution.

Distribute in 5 and 10 c c quantities in test tubes and incubate at 37° C

Ruge Solution (Used to dehemoglobinize thick drop preparations) —

Formol	2 c c
Acetic acid	1 c c
Distilled water	100 c c

S

Saisawa-Sugawara Stain (For microfilariae) (Foshay, 1947) —

Solution A.—

Tannic acid	5 0 Gm
Distilled water, q s	100 c c

Dissolve with minimal heat When cool, filter and add, in the following order

Fe_2Cl_6, 40% aqueous solution	1 5 c c
Formalin	2 0 c c
NaOH, 10% aqueous solution	*1 5* c.c.

Shake well It should have an indigo color The whiter the tannic acid, the better the mordant

Solution B —

$AgNO_3$	2 0 Gm
Distilled water, q s	100 c c

Dissolve

Place 10 c c in a beaker

While shaking, add strong ammonia water, drop by drop, until an opalescence appears and disappears Then add the remaining 90 c c and shake well It should show a brownish turbidity

If kept separately in well stoppered brown bottles, these solutions will remain useful for at least a month.

Procedure for Staining Blood Smears —

A small amount of each solution, shaken well, is filtered through filter paper just before smears are to be stained For smears previously stained with hematoxylin flood the area with filtrate of solution A for 5 to 8 minutes, the duration depending upon the depth of mordanting desired

Flood off the mordant with distilled water, and wash the slide in running tap water for 4 or 5 minutes

Again flush the slide with distilled water

Flood it then with solution B Tilt the slide back and forth over a white surface until it develops an evenly distributed deep orange brown color This requires 3 to 20 seconds

As soon as the desired color develops, quickly wash off the solution with distilled water, and again wash the slide for several minutes in running tap water

Dry in the air and mount in Clarite

When this method is applied to dried smears, hydrate them for 15 to 30 minutes in water and allow them to just become dry in the air before mordanting

Schaudinn Fixative —

Saturated aqueous mercuric chloride solution	200 c c
95% ethyl alcohol	100 c c

Mix and add before using, 2 to 5 c c of glacial acetic acid. Some authors recommend different percentages of acetic acid (12 to 15%)

Seneca Medium (For cultivation of Leishmania and *T cruzi*) —

(1) Dissolve 50 Gm Bacto-beef extract in 1 000 c c of distilled water Heat at 50° C for ½ hour and then for 5 minutes at 80° C Filter and add

Neo peptone	20 parts
Agar (Nobel)	20 parts
Sodium chloride	5 parts

Adjust the reaction to pH 7 2 to 7 4 and sterilize in an autoclave at 15 pounds pressure for 20 minutes

Cool and add defibrinated rabbit blood to a concentration of 10 per cent

(2) *Extract of Liver and Eggs*

Emulsify 4 eggs in a sterile flask containing glass beads Add 50 c c of the following solution

Sodium chloride	0 02 Gm
Calcium chloride	0 02 Gm
Potassium chloride	0 02 Gm
Sodium bicarbonate	0 02 Gm
Distilled water	100 c c

Mix well filter distribute in test tubes or flasks and sterilize at 90° C for 10 minutes then at 10 pounds pressure Lower the pressure slowly to prevent formation of air bubbles

Cover the culture with 0 5% sterile liver extract in physiologic saline solution

Incubate 24 hours to test for sterility

Simons Solution (For rapid staining of thick drops) —

Methylene blue	0 6 Gm
Sodium chloride	1 8 Gm
Sodium citrate	3 0 Gm
Saponin (Rhone Poulenc)	2 0 Gm
15% formol	12 0 c c

Stevenel Stain (Used in the Boye technic of staining thick drops of blood) —

Medicinal methylene blue	1 Gm
Potassium permanganate	1 5 Gm
Distilled water	150 c c

Dissolve the methylene blue and the permanganate in 75 c c of the distilled water separately and mix in a flask A precipitate will form Place in a water bath for ½ hour until the precipitate redissolves Filter The stain will be a dark violet color

T

Tanabe and Chiba Medium (For cultivation of *E histolytica*) —

Agar	10 Gm.
Asparagin	1 Gm.
Ringer solution	1,000 c c

Sterilize in an autoclave at 15 pounds pressure for 30 minutes Slant while still hot and allow to solidify

Cover the surface of the slants with Ringer solution containing 5 per cent sterile rabbit serum

Add a small quantity of sterile dried rice starch before inoculating the *medium*

Torres Medium (For cultivation of *T. cruzi*) —

Peptone	5 Gm
Sodium chloride	7 Gm
Beef broth	100 c c

Dissolve 5 Gm of Bacto beef (Difco) in 100 c c of distilled water in a water bath at 55° C for 1 hour to prepare the beef broth

Add the salt and the peptone while hot

Filter and adjust the reaction to pH 6 55 to 7 18

Distribute in tubes and sterilize

Incubate in a dark place at 22° to 25° C

Subculturing is difficult

Tsuchiya Method (For cultivation of amebae) —

Nutrient Broth —

Dissolve 3 Gm meat extract
and 5 Gm *sodium chloride*
in 1,000 c c of distilled water

Adjust the reaction to pH 7 0 and sterilize in an autoclave at 15 pounds pressure for 30 minutes *The pH of the medium within a range of 6 8 to 7 4 also answers the purpose,* although the optimum pH is 7 0

"S C" mixture is a thoroughly triturated mixture of rice starch and animal *charcoal in the proportion of 2 1 by volume A small amount of the mixture is placed* loosely in a small vial and sterilized by dry heat at 180° C for 45 minutes

For use, add two 4 mm loopfuls of the "S C" mixture to 8 c c of the sterile nutrient *broth*

V

Van Cleave and Ross Method (For reclaiming dried zoological specimens) —

A 0 25 to 0 5 per cent solution of commercial trisodium phosphate in distilled water is effective in restoring the appearance of specimens Warmed solutions are more rapid in action than cold The maximum effect is obtained in about 1 hour, with small or delicate objects

W

Water, Neutral Distilled —

The method of choice is that using hematoxylin as an indicator and 1% potassium carbonate and 1% hydrochloric acid as neutralizing agents Refer to Chapter 68

Neutrality of water may also be attained by using buffer capsules or buffer solutions

Acid Solutions —

M/15 NaH_2PO_4	9 2 Gm per liter
M/15 KH_2PO_4	9 07 Gm per liter

Alkaline Solution.—

M/15 Na_2HPO_4 ---- 9 5 Gm per liter

pH	Acid Solution		Alkaline Solution	Water to Make
7 0	38 9 c c	+	61 1 c c	900 c c
7 2	28 0 c c	+	72 0 c c	900 c c

Distribute in glass containers and cover the surface with a layer of mineral oil to prevent entrance *of atmospheric carbon dioxide*

Wenyon Medium (For cultivation of *Emb intestinalis* and Trichomonas) —

2% nutrient agar, pH 7 6	30 c c
0 85% sodium chloride solution, pH 7 6	270 c c

Add the agar to the sodium chloride solution mix well, and distribute in 10 c c quantities

Sterilize in an autoclave at 15 pounds pressure for 20 minutes

When the medium cools to 50° C add 20 drops of defibrinated rabbit blood to each tube Control the sterility by incubating for 24 hours at 37° C and observing for growth

Wright Stain.—

See Chapter 68

Y

Young and Van Sant Medium (For cultivation of *L donovani* from peripheral blood) —

Obtain 10 c c of venous blood in a sterile syringe containing 2 c c of Locke solution

Place in a flask containing 50 to 70 c c of Locke solution

Mix well and place in two 50 c c centrifuge tubes

Centrifuge for 5 minutes at 750 r p m until the red cells have been completely sedimented Decant the supernatant fluid and centrifuge again for 5 minutes at approximately 1,375 r p m

Place the sediment in tubes containing NNN medium with rabbit blood pH 7 6

Incubate at 22° C

The flagellates will appear in the medium between the tenth and twelfth days

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